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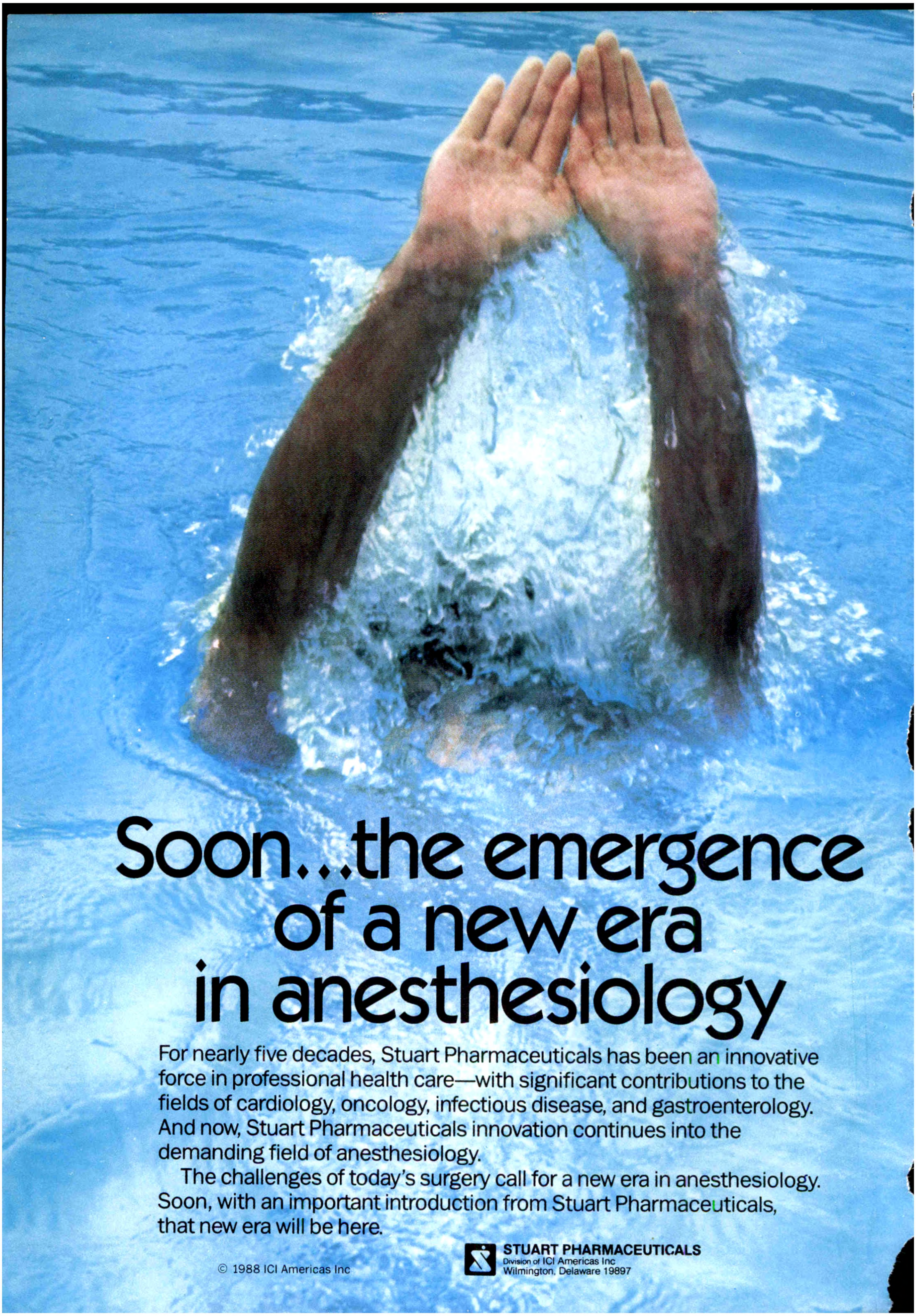

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Anesthesia and Analgesia

Contents

Volume 69, Number 5, November 1989

EDITORIAL

Is Anesthesia Therapeutic? *Stanley H. Rosenbaum and Paul G. Barash* 555

SCIENTIFIC ARTICLES

Thoracic Epidural Anesthesia and Central Hemodynamics in Patients with Unstable Angina Pectoris *Sture Blomberg, Håkan Emanuelsson, and Sven-Erik Ricksten* 558

Acute Toxicity of Ropivacaine Compared with That of Bupivacaine *D. Bruce Scott, Alistair Lee, Denise Fagan, Geoffrey M. R. Bowler, Peter Bloomfield, and Rolf Lundh* 563

Growth of Allogeneic Sarcoma in Mice Subjected to Halothane Anesthesia and/or Surgical Stress *Biserka Radošević-Stašić, Marija Udović-Širola, Lovorka Stojanov, Ljubomir Ribarić, and Daniel Rukavina* 570

Effect of Isoflurane on the Extent of Myocardial Necrosis and on Systemic Hemodynamics, Regional Myocardial Blood Flow, and Regional Myocardial Metabolism in Dogs after Coronary Artery Occlusion *Richard F. Davis and Avner Sidi* 575

Role of Spinal Adenosine Receptors in Modulating the Hyperesthesia Produced by Spinal Glycine Receptor Antagonism *M. Sosnowski and T. L. Yaksh* 587

Spinal Anesthesia with Plain Bupivacaine 0.5%: Regression of Sensory and Motor Blockade with Different Temperatures of the Anesthetic Solution *Rudolf Stienstra, Mathieu Gielen, Frans van Poorten, and Jan Willem Kroon* 593

Abdominal Muscle Activity and Intraabdominal Pressure after Upper Abdominal Surgery *John E. Duggan and Gordon B. Drummond* 598

Transient Maternal Hypotension following Epidural Anesthesia *Elliot H. Philipson, Betty R. Kuhnert, Renato Pimentel, and Saeid B. Amini* 604

Bronchial Cuff Pressures of Double-Lumen Tubes *Jay B. Brodsky, Micheal O. Adkins, and David M. Gaba* 608

Intravenous Ranitidine Antagonizes Intense Atracurium-Induced Neuromuscular Blockade in Rats *Stuart C. Law, Iqbal M. Ramzan, Barbara W. Brandom, and D. Ryan Cook* 611

Postoperative Isolated Dysfunction of the Long Thoracic Nerve: A Rare Entity of Uncertain Etiology *John T. Martin* 614

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SCIENTIFIC ARTICLES—continued

Incidence of Venous Air Embolism during Cesarean Section Is Unchanged by the Use of a 5 to 10° Head-Up Tilt — *Venkateswara R. Karuparthy, John W. Downing, Farkhanda J. Husain, Kelly G. Knape, Janna Blanchard, Dale Solomon, and Maurice S. Albin* — 620

Effect of Rate of Injection on the Neuromuscular Block Produced by Vecuronium — *Stanley A. Feldman, Neil Soni, and Maryke A. Kraayenbrink* — 624

A Comparative Study of Methods of Detection of Esophageal Intubation — *Sam T. Sum-Ping, Mahesh P. Mehta, and John M. Anderton* — 627

SPECIAL ARTICLE

A Cardiogenic Hypertensive Chemoreflex — *Thomas N. James* — 633

REVIEW ARTICLE

The Jehovah's Witness Patient: Considerations for the Anesthesiologist — *Kirk T. Benson* — 647

TECHNICAL COMMUNICATION

Isoflurane Uptake and Elimination Are Delayed by Absorption of Anesthetic by the Scimed Membrane Oxygenator — *Richard C. Stern, Carey I. Weiss, Joe Henry Steinbach, and Alex S. Evers* — 657

CLINICAL REPORTS

Esmolol in the Management of Epinephrine- and Cocaine-Induced Cardiovascular Toxicity — *S. Pollan and M. Tadjziechy* — 663

Differential Effect of Prostaglandin E_1 and Sodium Nitroprusside on Intrapulmonary Shunt Fraction in a Cardiac Transplantation Patient — *Paul M. Heerdt and Lawrence L. Yee* — 665

Oscillometric Blood Pressure Determination from the Adult Thumb Using an Infant Cuff — *Michael S. Gorback, Timothy J. Quill, Edmund C. Bloch, and Daniel A. Graubert* — 668

Interpleural Analgesia in Treatment of Upper Extremity Reflex Sympathetic Dystrophy — *Finn Reiestad, William B. McIlvaine, Lars Kvalheim, Trond Stokke, and Bjorg Pettersen* — 671

Contaminated Oxygen Cylinder — *Lewis A. Coveler and Rodney C. Lester* — 674

T-Wave Changes Associated with Electroconvulsive Therapy — *Georges F. Khoury and Constantino Benedetti* — 677

Comparison of the Effects of Oral Famotidine and Ranitidine on Gastric Volume and pH — *Stevin A. Dubin, Paul I. Silverstein, Marsha L. Wakefield, and Holly G. Jense* — 680

An Anaphylactic Reaction to Fibrin Glue — *Leslie Newberg Milde* — 684

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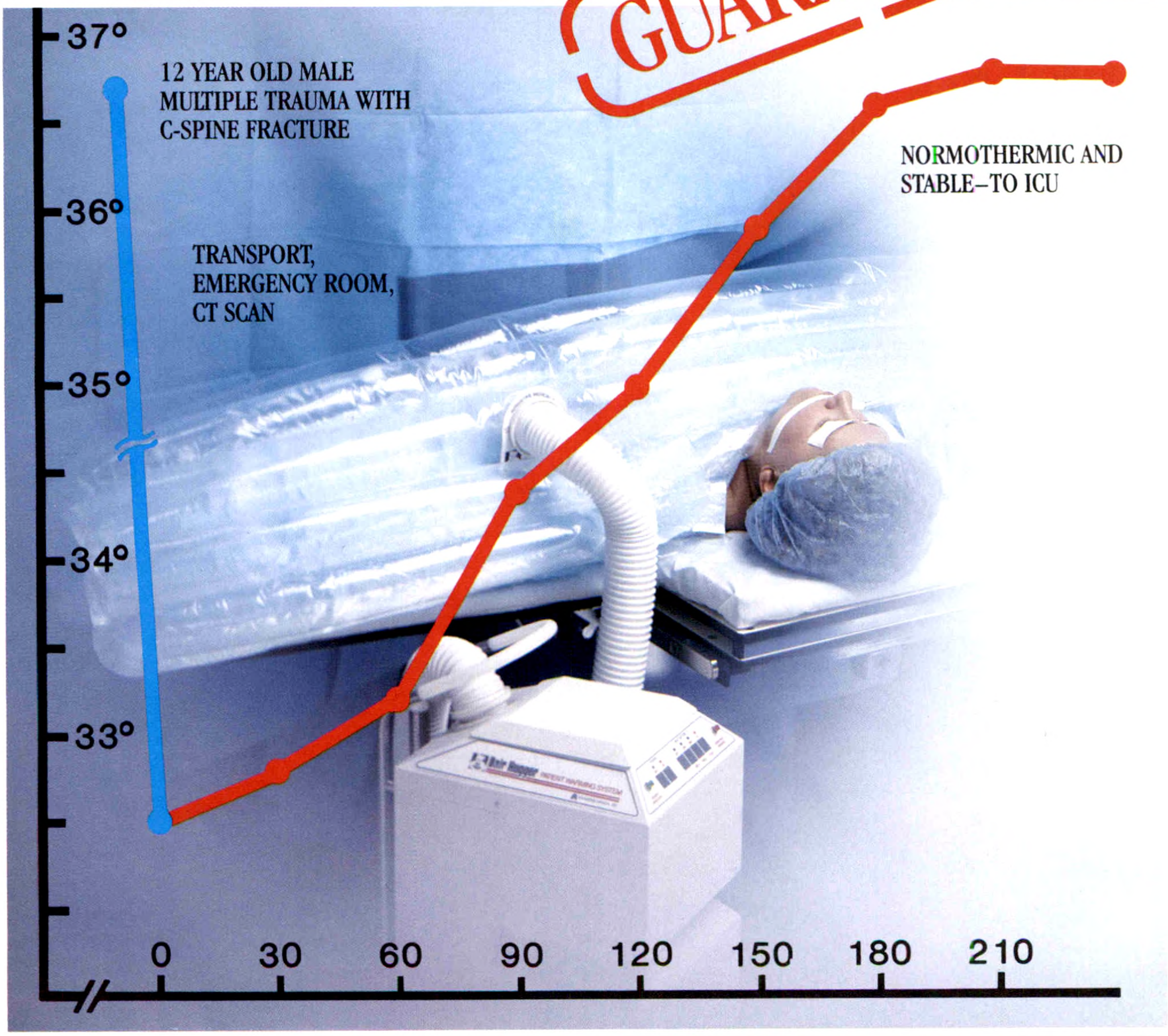

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CLINICAL REPORTS—continued

Effects of Lidocaine, Succinylcholine, and Tracheal Intubation on Intraocular Pressure in Children Anesthetized with Halothane-Nitrous Oxide — *Louise O. Warner, Don L. Bremer, Patricia J. Davidson, Gary L. Rogers, and Thomas P. Beach* 687

LETTERS TO THE EDITOR

"Just a Little Bit More" — *Roger E. Hofer, Robert L. Lennon, and Paul Didier* 691

Central Nervous System Effects of Magnesium — *Michele D. Szabo and Gregory Crosby* 691

Poststernotomy Neuralgia: A New Pain Syndrome — *Donald P. Todd* 692

In Response — *Ray J. Defalque and Joel J. Bromley* 692

BOOK REVIEWS

Molecular and Cellular Mechanisms of Septic Shock, Progress in Clinical and Biological Research, Volume 286 — *Daniel L. Traber* 693

Surgery for Anaesthetists — *Carter M. Ballinger* 693

On Chloroform and Other Anaesthetics: Their Action and Administration — *Samuel Tirer* 694

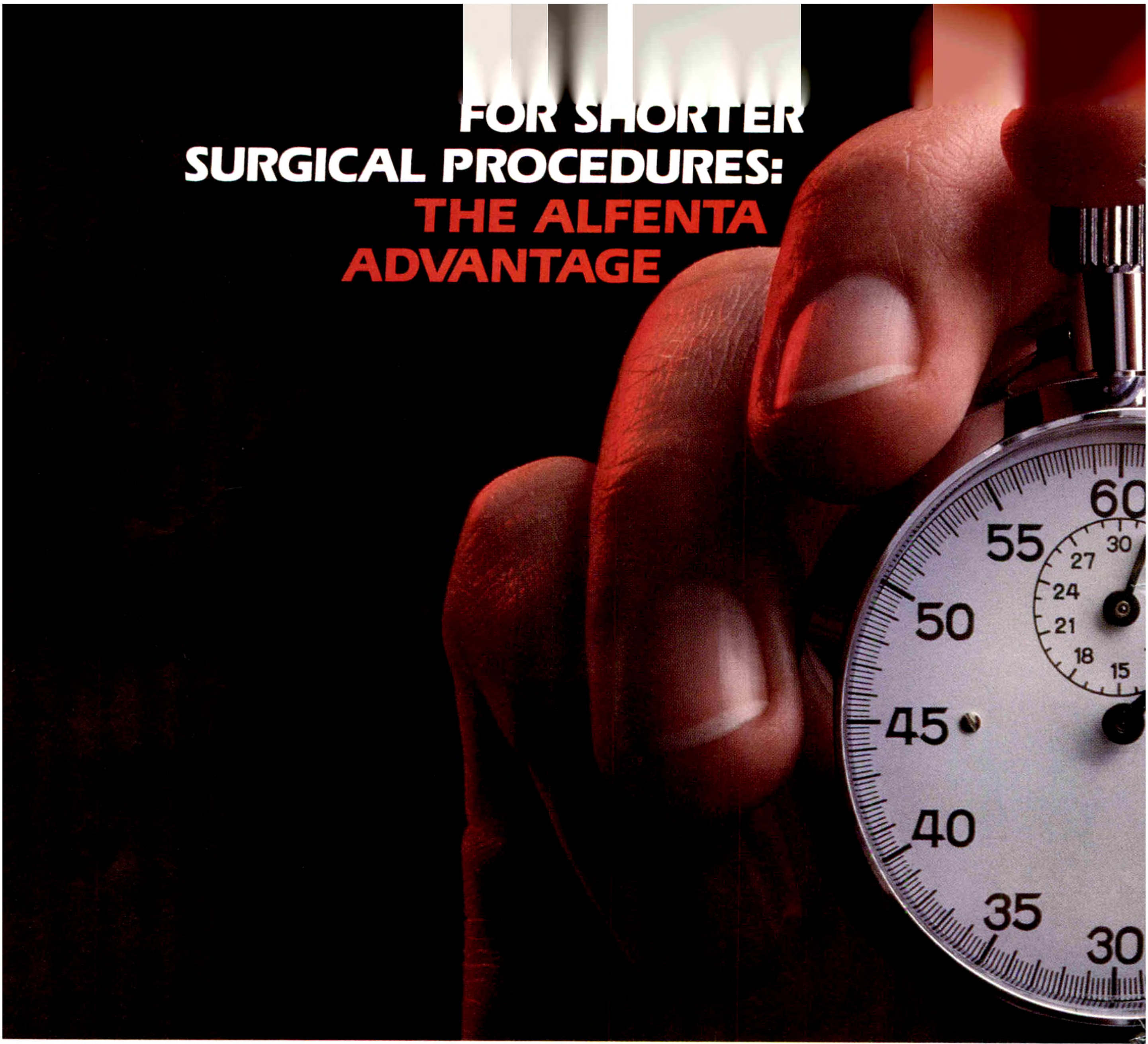
Risk and Outcome in Anesthesia — *William Gild* 694

Cardiac Monitoring, Anesthesiology Clinics of North America, December 1988 — *James H. Diaz* 695

Anesthesia and the Lung — *Julian M. Goldman and Philip Brown* 695

Cardiovascular Anesthesia and Postoperative Care (2nd edition) — *Joseph J. Quinlan* 696

Books Received 696



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PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Editorial

Is Anesthesia Therapeutic?

Stanley H. Rosenbaum, MD and Paul G. Barash, MD

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—treatment of angina. HEART, ANGINA—treatment with epidural block.

The discovery and application of anesthesia is one of medicine's most important contributions to humanity. Despite its impact, modern anesthesia is often regarded as merely a technique for facilitating surgical procedures. Other than its effect on pain relief, can anesthesia be regarded as truly therapeutic? Blomberg and colleagues, in this issue of *Anesthesia and Analgesia*, detail a study in which patients with severe coronary artery disease and unrelenting angina pectoris derive a significant *therapeutic* effect from thoracic epidural anesthesia (TEA) (1).

Sympathetic blockade produced by a high epidural anesthetic has been known for some time to affect coronary blood flow. Sivarajan et al. found that in monkeys with normal coronary arteries, TEA decreases both mean blood pressure and coronary blood flow (2). Despite the large decrease in coronary blood flow, their data indicated that perfusion was adequately matched to myocardial oxygen demand. Vik-mo et al. subsequently observed in a study of dogs that TEA reverses the ST-segment changes induced by experimental coronary artery occlusion (3). Klassen et al., also employing a canine model of acute coronary occlusion, demonstrated that the endocardial/epicardial blood flow ratio increased following TEA (4). Using a similar model, Davis et al. confirmed these observations (5). More importantly, Davis et al. discovered that not only did thoracic sympathetic blockade enhance regional myocardial blood flow, but it also reduced the anatomic extent of the experimentally induced infarction. Three subsequent studies have evaluated the circulatory effects of TEA in patients with significant coronary artery disease undergoing noncardiac operations (6–8). These perioperative clinical investigations have shown that in patients with ischemic heart disease TEA results in decreases in the indices of both myocardial oxygen supply and demand.

Therefore, it was reasonable for Blomberg et al. to hypothesize that a beneficial effect of TEA might be observed in cardiac patients in a coronary care unit environment. In this provocative study of the benefits of TEA in the treatment of myocardial ischemia in patients with severe angina pectoris unresponsive to multiple medical regimens, TEA achieved more than mere control of pain. Thoracic epidural anesthesia reduced myocardial oxygen demand by decreasing systolic arterial blood pressure, heart rate, and pulmonary capillary wedge pressure without significant changes in coronary perfusion pressure or cardiac output. The authors hypothesize that the beneficial results of TEA in this unique setting derive from alterations in myocardial oxygen supply–demand relationships, as well as a more favorable transmural redistribution of coronary blood flow.

Admittedly, the report by Blomberg et al. can be regarded only as preliminary work on the clinical value of TEA for patients in a coronary care unit. Although TEA is relatively easy to administer, a word of caution or perhaps more appropriately a statement of caveat emptor is justified. The authors do not give us detailed data that would assure us that the use of nitroglycerin, calcium channel blockers, beta blockers, and analgesics were genuinely optimized before the administration of TEA. Measurement of myocardial lactate extraction, as well as documentation of ischemia by noninvasive methods (e.g., echocardiography, radionuclide angiography, etc.), must be done

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before we can be certain that the benefits reported with TEA are truly more than pain relief. The role of the systemic absorption of the local anesthetic agent needs to be clarified, particularly given that Watwil et al. observed a significant hemodynamic effect from vascular absorption of the drug following TEA administration (9). Finally, TEA is not without complications. Is the use of TEA justified in a group of patients to whom drug(s) with anticoagulant properties are administered? How well can a patient with unstable angina respond to total sympathetic blockade secondary to unintentional subarachnoid injection (9)? Is it possible that an adverse hemodynamic response will occur when TEA is administered to patients receiving antianginal medications such as nitrates, beta blockers, and/or calcium channel blockers (7,10,11)? Commenting on the clinical implications of a study that used TEA (4), Merin expressed analogous reservations (12). He appropriately made the point that whereas autoregulation is efficient in the normal heart, the control of coronary circulation in patients with ischemic heart disease is dependent on blood pressure. Thus, the effects of acute, significant, and often unpredictable decreases in the systemic blood pressure can have deleterious consequences.

Despite the above, the suggestion of therapeutic benefit has been made, and a body of knowledge exists that proposes several possible mechanisms for the salutary effects of TEA seen in Blomberg's patients. On a global basis, TEA decreases myocardial oxygen demand (2,5–8). Reduction in wall stress, heart rate, and inotropy have all been reported. Despite the potential for a "coronary steal," improvements in perfusion to ischemic areas have been observed (4,5,13,14). This effect may be on the basis of reduced left ventricular wall pressure with a redistribution of blood flow to the subendocardial layer. Conversely, thoracic sympathetic blockade decreases cardiac autonomic tone and thus may favorably alter the endo/epicardial blood flow ratio. However, this mechanism is thought to be only a minor determinant of transmural coronary blood flow (3,12,15). TEA also alters myocardial metabolism and reduces the uptake of catecholamines (3,6,7). Acute sympathetic blockade has been hypothesized to inhibit lipolysis within the ischemic area, thereby decreasing regional myocardial oxygen consumption and reducing the severity of the ischemic injury. Finally, the possible effect of sympathetic blockade on coronary vasoconstriction distal to coronary stenoses is apt to be involved. Heusch et al. have shown that sympathetic poststenotic vasoconstriction can be blocked by epidural anesthesia (13,14). Poststenotic ischemia may activate further sympathetic discharge via spinal reflexes, and produce a positive feedback mechanism leading to a vicious cycle of progressive vasoconstriction and worsening of myocardial ischemia. The persistent therapeutic effect of TEA in alleviating ischemia may be due to blocking of this feedback mechanism.

In recent years anesthesiologists have brought knowledge, equipment, and procedures to parts of the hospital where general and/or regional anesthesia, without surgery or the presence of surgeons, is of benefit to patients. The work reported by Blomberg et al. may lead to a further expansion of the role of anesthesiologists. We are starting to see the use of classic anesthetic techniques in novel settings as a therapy for preservation of the jeopardized myocardium (16). If additional data demonstrate the empirical value of these techniques, the mission of the anesthesiologist will expand and the continuing contributions of our specialty to humanity will add to the importance of the pivotal discoveries of Drs. Long, Morton, Wells, and Koller.

References

1. Blomberg S, Emanuelsson H, Ricksten S-E. Thoracic epidural anesthesia and central hemodynamics in patients with unstable angina pectoris. Anesth Analg 1989;69:558–62.
2. Sivarajan M, Amory DW, Lindbloom LE. Systemic and regional blood flow during epidural anesthesia without epinephrine in the rhesus monkey. Anesthesiology 1976;45:300–10.
3. Vik-mo H, Ottesen S, Renck H. Cardiac effects of thoracic epidural analgesia before and during acute coronary artery occlusion in open-chest dogs. Scand J Clin Lab Invest 1978; 38:737–46.
4. Klassen GA, Bramwell RS, Bromage PR, Zborowska-Sluis DT. Effect of acute sympathectomy by epidural anesthesia on the canine coronary circulation. Anesthesiology 1980;52:8–15.
5. Davis RF, DeBoer LWV, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery occlusion in dogs. Anesth Analg 1986;65:711–7.
6. Reiz S, Nath S, Rais O. Effects of thoracic epidural block and prenalterol on coronary vascular resistance and myocardial metabolism in patients with coronary artery disease. Acta Anaesthesiol Scand 1980;24:11–6.
7. Reiz S, Haggmark S, Rydvall A, Ostman M. Beta-blockers and thoracic epidural analgesia. Cardioprotective and synergistic effects. Acta Anaesthesiol Scand 1982;76(Suppl):54–61.
8. Hasenbos M, Liem TH, Kerkkamp H, Gielen M. The influence of high thoracic epidural analgesia on the cardiovascular system. Acta Anaesthesiol Belg 1988;39:49–54.
9. Wattwil M, Sundberg A, Arvill A, Lennquist C. Circulatory changes during high thoracic epidural anaesthesia—influence of sympathetic block and of systemic effect of the local anaesthetic. Acta Anaesthesiol Scand 1985;29:849–55.
10. Blomberg S, Ricksten SE. Thoracic epidural anaesthesia in conscious and anaesthetized rats. Effects on central haemodynamics compared to cardiac beta adrenoreceptor and ganglionic blockade. Acta Anaesthesiol Scand 1988;32:166–72.

11. Hotvedt R, Refsum H, Platou ES. Cardiac electrophysiological and hemodynamic effects of beta-adrenoceptor blockade and thoracic epidural analgesia in the dog. Anesth Analg 1984; 63:817–24.
12. Merin R. Clinical implications of effects of thoracic epidural anesthesia on endocardial/epicardial flow distribution ratio are not justified. Anesthesiology 1980;53:349–51.
13. Heusch G, Deussen A, Thamer V. Cardiac sympathetic nerve activity and progressive vasoconstriction distal to coronary stenoses: feed-back aggravation of myocardial ischemia. J Auton Nerv Syst 1985;13:311–26.
14. Heusch G, Schipke J, Thamer V. Sympathetic mechanism i poststenotic myocardial ischemia. J Cardiovasc Pharmac 1986;8(Suppl 3):S33–S40.
15. Schwartz PJ, Stone HL. Tonic influence of the sympatheti nervous system on myocardial reactive hyperemia and o coronary blood flow distribution in dogs. Circ Res 197 41:51–8.
16. De Bruijn NP, Hlatky MA, Jacobs JR, et al. General anesthesi during percutaneous transluminary coronary angioplasty fo acute myocardial infarction: results of a randomized controlle clinical trial. Anesth Analg 1989;68:201–7.

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Thoracic Epidural Anesthesia and Central Hemodynamics in Patients with Unstable Angina Pectoris

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BLOMBERG S, EMANUELSSON H, RICKSTEN S-E. Thoracic epidural anesthesia and central hemodynamics in patients with unstable angina pectoris. Anesth Analg 1989;69:558–62.

The effects of high thoracic epidural anesthesia (TEA) on central hemodynamics as measured by pulmonary arterial catheterization were studied in nine patients with severe coronary artery disease and unstable angina pectoris. The patients were also treated with a combination of beta-blockers, calcium antagonists, and nitrates, as well as salicylates, low-dose heparin, and nitroglycerin infusion for >24 hr. Management of pain with high TEA was started with the bolus epidural injection of 4.3 ± 0.2 mL bupivacaine (5 mg/mL), which induced a sympathetic blockade from Th_{1-8}. *During ischemic chest pain, pulmonary artery and pulmonary capillary wedge pressures were significantly increased. TEA, while relieving the chest pain, significantly decreased systolic arterial blood pressure, heart rate, and pulmonary artery and pulmonary capillary wedge pressures, without any significant changes in coronary perfusion pressure, cardiac output, stroke volume, and systemic or pulmonary vascular resistances. In some patients, ST-segment depression was less pronounced during TEA. Thus, during ischemic chest pain, TEA has beneficial effects on the major determinants of myocardial oxygen consumption, without jeopardizing coronary perfusion pressure. TEA may therefore favorably alter the oxygen supply/demand ratio within ischemic myocardial areas.*

Key Words: ANESTHETIC TECHNIQUES—epidural. HEART, ISCHEMIA. PAIN, ANGINA.

Thoracic epidural anesthesia (TEA), including a blockade of the cardiac sympathetic afferents and efferents, may have beneficial effects on the ischemic myocardium. During experimental myocardial ischemia in anesthetized animals, TEA reduces the major determinants of myocardial oxygen consumption, i.e., mean arterial pressure, heart rate, and contractility (1,2). Furthermore, during coronary occlusion in anesthetized animals, TEA improves the distribution of regional myocardial blood flow by increasing the endocardial-to-epicardial blood flow ratio (2,3), while also reducing the incidence of malignant ventricular arrhythmias (4), decreasing the degree of myocardial ischemia (1,2), and reducing myocardial infarct size (2). Thus, TEA exerts a cardio-protective effect during experimental myocardial ischemia by improving the myocardial oxygen supply/demand ratio.

Thoracic epidural anesthesia with local anesthetics is effective in the treatment of severe, ischemic chest pain in patients with acute myocardial infarction (5,6), while devoid of unwanted side effects such as hypotension or severe bradycardia. Furthermore, it has recently been shown that TEA may also effectively control pain in patients with unstable angina pectoris with ischemic chest pain at rest, that is, angina pectoris resistant to conventional medical therapy, including nitroglycerin infusion (7).

The aim of the present investigation was to study the effects of TEA on central hemodynamics in patients with severe coronary artery disease and ischemic chest pain at rest.

Material and Methods

The study was approved by the Human Ethics Committee of the University of Gothenburg. Nine patients, eight men and one woman, with a mean age of

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Table 1. Patient Demographics

			Previous history			Coronary angiography		Medical treatment					
Patient No.	Sex (M/F)	Age (years)	MI	Coronary bypass surgery	PTCA	Main stem stenosis	No. of obstructed vessels	Beta-blockers	Ca^{++} antagonists	Long-acting nitrates	Short-acting nitrates	Salicylates	Hepari
1	F	72	3	–	–	–	?	+	+	+	+	–	–
2	M	78	2	–	–	–	?	–	+	+	+	–	–
3	M	69	4	–	–	–	3	+	–	+	+	–	+
4	M	57	2	1	–	–	3	+	+	+	+	–	+
5	M	69	1	–	–	+	3	+	+	–	+	–	–
6	M	69	–	–	1	–	1	+	+	+	+	+	+
7	M	74	–	1	–	–	3	+	+	+	+	+	+
8	M	59	3	–	–	–	3	+	+	+	+	–	+
9	M	54	1	–	–	–	1	+	–	–	+	–	–

MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty.

67 ± 3 years, took part in the study after giving their informed consent. All patients were treated in a coronary care unit because of typical, intermittent, or continuous chest pain at rest not caused by acute myocardial infarction, as judged by 12-lead standard electrocardiogram (ECG) and/or increased blood levels of cardiac enzymes. The medical management of these patients consisted of combinations of beta-blockers, calcium antagonists, nitrates, salicylates, and low dose heparin (Table 1). In addition, all patients were treated with nitroglycerin infusions for >24 hr. Pain treatment with high TEA was initiated in all patients when several attempts to discontinue the nitroglycerin infusion had failed, as indicated by recurrence of chest pain or more severe chest pain. The clinical history, angiographic findings, and pharmacological treatments are summarized in Table 1.

A Portex epidural catheter was inserted through one of the second to fifth thoracic vertebral interspaces, employing the median approach and the loss-of-resistance technique with minimal amounts of normal saline. The aim was to place the tip of the catheter at the level of the upper thoracic vertebrae. In the supine position, a test dose of 2 mL of bupivacaine (5 mg/mL) was injected epidurally to exclude intradural administration of the local anesthetic. Five minutes later, depending on the anesthetic spread of the bolus dose, 1 to 3 mL of bupivacaine was injected, to induce a blockade of at least the cardiac sympathetic segments (Th_{1-5}). The extent of blockade was evaluated 20 min after the final dose by measuring the extent of loss of temperature discrimination ability, using ether applied to the skin of the chest wall. Before the effect of the first cardiac sympathetic blockade had worn off, the nitroglycerin infusion was gradually discontinued within 3 hr. During this period and thereafter, patients were given the initially titrated epidural bolus dose of bupivacaine with each new attack of chest pain. The duration of epidural analgesia was determined in eacl patient.

Experimental Procedure and Protocol

Within 12 hr after the start of TEA treatment, a pulmonary artery catheter (via the internal jugula vein) and a radial artery catheter were inserted. Th effects of the initial dose of TEA on central hemodynamics were studied in the supine position withou ischemic chest pain ($n = 8$) and during myocardia ischemia ($n = 9$). The patients had not been under th influence of regional anesthesia for at least 5 h an were able to discriminate temperature at the time o the hemodynamic measurements. Systolic (SAP), diastolic (DAP), and mean arterial pressures (MAP were measured together with pulmonary arteria (SPAP, DPAP, and MPAP), pulmonary capillar wedge (PCWP), and right atrial (RAP) pressures Cardiac output (CO) was measured in triplicate b the thermodilution technique. Cardiac index (CI $L \cdot min^{-1} \cdot m^{-2}$) coronary perfusion pressure (CPP DAP-PCWP), stroke volume index (SVI, mL/m^2) systemic (SVR) and pulmonary vascular (PVR) resistances ($mm\ Hg \cdot min \cdot L^{-1}$) as well as systemic (SVRI and pulmonary (PVRI) vascular resistance indice ($mm\ Hg \cdot min \cdot L^{-1} \cdot m^2$) were calculated using standar formulas. A 12-lead standard ECG was recorde before and after induction of TEA.

The values are expressed as mean values ± SEM For statistical analyses, a paired Student's *t*-test wa used. A value of $P < 0.05$ was considered to b statistically significant.

Results

An average amount of 4.3 ± 0.2 mL of bupivacain induced a blockade of the upper thoracic segment

Table 2. Effects of TEA on Central Hemodynamics during a Pain-Free Interval and during Ischemic Chest Pain

	No pain	TEA	Ischemic chest pain	TEA
SAP (mm Hg)	146 ± 10	141 ± 9	159 ± 11	139 ± 9**
MAP (mm Hg)	82 ± 5	81 ± 5	94 ± 7	85 ± 6
DAP (mm Hg)	57 ± 3	56 ± 4	63 ± 4	59 ± 5
SPAP (mm Hg)	20 ± 2	21 ± 1	29 ± 2*	22 ± 2**
MPAP (mm Hg)	12 ± 1	12 ± 1	18 ± 2*	13 ± 1**
DPAP (mm Hg)	7 ± 1	6.1 ± 1.1	11.9 ± 1.3*	7.7 ± 1.2**
PCWP (mm Hg)	7 ± 1	5.8 ± 1.3	11.6 ± 1.7*	6.7 ± 1.3**
RAP (mm Hg)	2 ± 1	1.3 ± 0.4	1.1 ± 0.9	0.1 ± 1.3
CPP (mm Hg)	50 ± 4	51 ± 4	52 ± 4	52 ± 4
CO (L/min)	5.7 ± 0.5	5.4 ± 0.5	6.1 ± 0.6	6.1 ± 0.6
CI (L·min^{-1}·m^{-2})	3.0 ± 0.2	2.8 ± 0.2	3.1 ± 0.3	3.2 ± 0.3
HR (beats/min)	65 ± 3	59 ± 3	68 ± 4	63 ± 4**
SV (mL/beat)	89 ± 7	93 ± 8	89 ± 8	99 ± 11
SVI (mL·beat^{-1}·m^{-2})	46 ± 3	49 ± 8	47 ± 4	52 ± 5
SVR (mm Hg·min·L^{-1})	15 ± 1.1	15 ± 1.4	16 ± 1.2	15 ± 1.2
SVRI (mm Hg·min·L^{-1}·m^{2})	28 ± 2.1	29 ± 1.9	30 ± 2.2	28 ± 2.4
PVR (mm Hg·min·L^{-1})	0.9 ± 0.2	1.3 ± 0.2	1.3 ± 0.3	1.3 ± 0.2
PVRI (mm Hg·min·L^{-1}·m^{2})	1.7 ± 0.3	2.4 ± 0.3	2.5 ± 0.5	2.2 ± 0.3

Values are mean ± SEM.
*Ischemic pain vs no pain = $P < 0.05$.
**TEA versus ischemic pain = $P < 0.05$.

with a mean rostral spread to $Th_{1.4 \pm 0.3}$ and a mean caudad spread to $Th_{8.3 \pm 0.4}$. The mean duration of the analgesia was 99 ± 5 min.

Under basal conditions (i.e., during rest without ischemic chest pain) high TEA was not associated with changes in measured hemodynamic variables (Table 2). Two patients (2 and 8) had ST-segment depressions on ECG at basal conditions that remained unchanged during TEA.

Measurements were also performed in all patients during ongoing chest pain. In this situation, SPAP, MPAP, DPAP, and PCWP increased significantly, by 37% ($P < 0.02$), 48% ($P < 0.05$), 56% ($P < 0.05$), and 59% ($P < 0.05$), respectively, compared to the pain-free control situation, while other hemodynamic variables remained unchanged. During ischemic chest pain, ST-segment depression was seen also in patient 7, and in patient 8 the ST-segment depression became more pronounced.

During the ischemic chest pain that spontaneously developed at rest, high TEA induced reductions in heart rate (−7%), SAP (−13%), SPAP (−24%), MPAP (−28%), DPAP (−35%), and PCWP (−42%), but no significant changes in MAP, DAP, CPP, CI, SVI, SVRI, or PVRI. During TEA, ST-segment depression was less pronounced in patients 7 and 8. In all patients, chest pain subsided within 10 min after induction of TEA.

Discussion

Unstable angina pectoris is a heterogeneous clinical syndrome with respect to the prevailing pathogenic mechanism and the underlying severity of coronary artery disease (8). Patients with unstable angina pectoris whose pain persists with bed rest, and those with preceding stable angina pectoris or myocardial infarction, are at high risk of developing acute myocardial infarction (9,10). In the present investigation all but two of our nine patients had a previous history of myocardial infarction(s). The severity of the underlying coronary artery disease (CAD) in these patients was further verified by the angiographic findings. Three patients had previously undergone coronary bypass surgery, and one patient had had coronary angioplasty.

In spite of maximal available therapy, including beta-blockers, calcium antagonists, nitrates, and anticoagulants, signs and symptoms of myocardial ischemia may persist, requiring a supplementary treatment for the control of pain while awaiting coronary angiography followed by surgery or angioplasty. In a recent study (7) we demonstrated that high TEA could effectively control pain in patients with unstable angina pectoris. In that study, nitroglycerin infusion was discontinued definitely within 3 hr after the introduction of TEA treatment and pain was thereafter controlled in the majority of the patients with TEA as the sole treatment. Furthermore, the pain-free intervals long outlasted the duration of the TEA, the average daily number of epidural injections decreased significantly with time, and 75% of the patients were fully mobilized within 24 hr after the start of the TEA treatment—results that, taken together, suggest that TEA may exert a stabilizing effect in patients with unstable angina pectoris.

In conscious, unmedicated, healthy humans it has been demonstrated that high TEA decreases arterial blood pressure, CO, stroke volume, heart rate, and myocardial contractility, due to cardiac sympathetic blockade (11–13). To our knowledge, there are no previous reports on the effects of high TEA, with selective blockade of the upper sympathetic segments, on central hemodynamics in patients with severe CAD and unstable angina. In the present study, TEA caused no significant changes in central hemodynamics during a pain-free interval. The lack of effect of TEA on CO could be explained by the fact that all but one of the patients were being treated with beta-blockers. Furthermore, TEA induced no change in systemic vascular resistance, probably due to the fact that the lowest thoracic and the lumbar preganglionic sympathetic fibers innervating hemodynamically important regions such as kidneys, large intestines, and skeletal muscles were not blocked.

During the spontaneous appearance of ischemic chest pain at rest, PCWP increased significantly, which most likely reflected an impairment of myocardial function. In this situation, high TEA resulted in a significant decrease in PCWP associated with significant decrease in SAP and heart rate while other variables were not affected. In other words, the analgesia was associated with reduction of the major determinants of myocardial oxygen demand without a hazardous decrease in CPP. Decreases in SAP and PCWP would also lead to a reduced wall tension with favorable effects on perfusion of subendocardial layers, which are most susceptible to myocardial ischemia in the presence of coronary stenosis (14).

An interesting observation was that TEA caused a clear-cut reduction in PCWP without a significant change in stroke volume, i.e., myocardial performance was improved by TEA. The decrease in preload of the left ventricle indicates that TEA caused dilation of systemic veins probably caused by the sympathetic blockade. In two patients (2 and 5; Figure 1) the decrease in preload was associated with a decrease in stroke volume, implying that the major effect of TEA in these two patients was a preload decrease caused by dilation of peripheral capacitance vessels. However, in the majority of the patients, the decrease in PCWP was accompanied by an increase in stroke volume, i.e., a leftward shift of the left ventricular function curve (Figure 1). This could be explained by a TEA-induced decrease in SVR as seen in the majority of the patients (Figure 2). One could also speculate that the maintenance of stroke volume during the cardiac sympathetic blockade, despite a decrease in

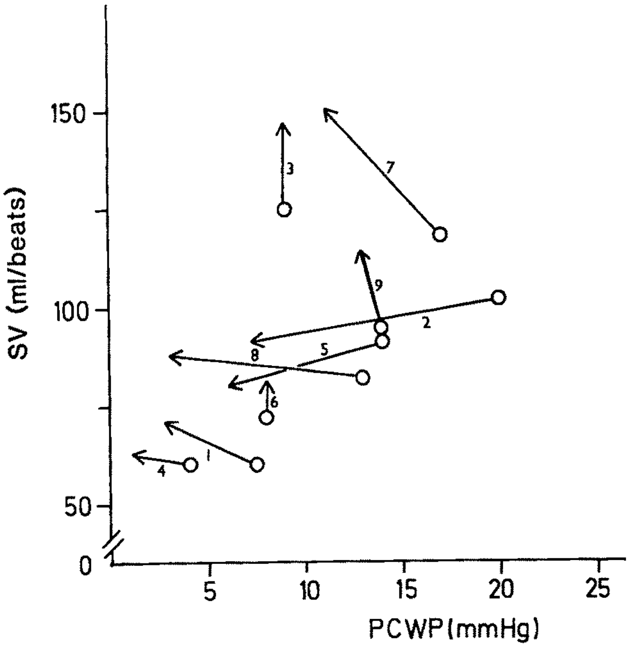

Figure 1. Effects in individual patients of thoracic epidural ane thesia (TEA) on stroke volume (SV) and pulmonary capilla wedge pressure (PCWP). The empty circles indicate values befo TEA, the arrows point to values during TEA.

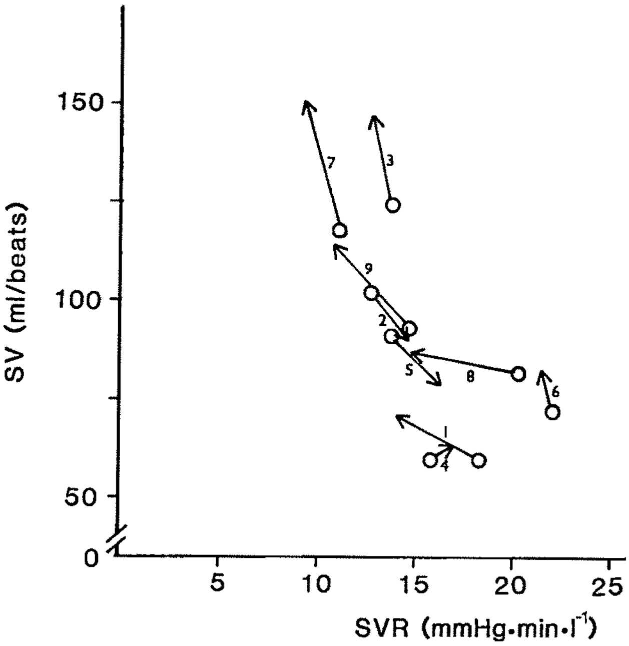

Figure 2. Effects in individual patients of thoracic epidural ane thesia (TEA) on stroke volume (SV) and systemic vascular resi tance (SVR). The empty circles indicate values before TEA, t arrows point to values during TEA.

preload, was due to an improved myocardial oxyge supply/demand ratio in the ischemic area(s). Thi possibility is supported by less pronounced ischemi ECG signs during TEA in two of the three patient who had ST-segment depression during chest pain

Painful or painless ischemic episodes in patients with unstable angina are caused by a transient impairment of regional coronary blood flow, which in turn is caused by dynamic stenosis of epicardial coronary arteries at the site of atherosclerotic plaques (15). It has been speculated that transient dynamic stenosis of epicardial arteries is caused by sympathetic nerves, stimulating postsynaptic alpha-adrenoceptors, and that the sympathetic nerves exert continuous restraint on the coronary smooth muscle (16). High TEA would decrease or even abolish the sympathetic stimulation of coronary alpha-adrenoceptors and, thus, theoretically, have the potential of improving regional myocardial blood flow. Reiz et al. (17), in four patients with CAD with no ischemic chest pain at rest, showed that coronary vascular resistance was reduced with TEA. However, in that study TEA was associated with extensive sympathetic blockade (Th_{1-12}) with a pronounced decrease in blood pressure. In that situation coronary vasodilation might well be an autoregulatory response to a decrease in perfusion pressure and not necessarily be caused by reduced sympathetic stimulation of the coronary vessels (18). A reduction in myocardial lactate extraction was also noted in the study by Reiz et al., indicating impairment of the oxygenation of certain parts of the myocardium (17). Thus, if the spread of TEA is too extensive and leads to substantial reduction in arterial blood pressure, there is a risk of myocardial ischemia, as the control of coronary circulation is principally pressure dependent in patients with CAD. In the present study, CPP (DAP-PCWP) was unchanged. Thus, high TEA may reduce myocardial oxygen demand in patients with unstable angina and ischemic chest pain without jeopardizing CPP.

In conclusion, TEA in patients with unstable angina resistant to conventional medical antianginal therapy had no effect on central hemodynamics at basal conditions, i.e., during a pain-free interval. During ischemic chest pain, however, TEA reduced SAP, heart rate, and PCWP, with no significant changes in CPP or other hemodynamic variables. TEA thus reduces the major determinants of myocardial oxygen consumption and may have antiischemic properties by favorably altering the myocardial oxygen demand/supply ratio of ischemic areas.

References

1. Vik-Mo H, Ottesen S, Renck H. Cardiac effects of thoracic epidural analgesia before and during acute coronary artery occlusion in open-chest dogs. Scand J Clin Lab Invest 1978; 38:737–46.
2. Davis RF, De Boer LWV, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery occlusion in dogs. Anesth Analg 1986;65 711–7.
3. Klassen GA, Bramwell RS, Bromage PR, Zborowska-Sluis DT. Effect of acute sympathectomy by epidural anesthesia on the canine coronary circulation. Anesthesiology 1980;52:8–15.
4. Blomberg S, Ricksten S-E. Thoracic epidural anaesthesia decreases the incidence of ventricular arrhythmias during acute myocardial ischemia in the anaesthetized rat. Acta Anaesthesiol Scand 1988;32:173–8.
5. Tevelenok YUA. Peridural anesthesia in the acute period of myocardial infarction. Anesteziol Reanimatol 1977;3:36–9.
6. Toft P, Jörgensen A. Continuous thoracic epidural analgesia for the control of pain in myocardial infarction. Intensive Care Med 1987;13:388–9.
7. Blomberg S, Curelaru I, Emanuelsson H, Herlitz J, Pontén J, Ricksten S-E. Thoracic epidural anaesthesia in patients with unstable angina pectoris. Eur Heart J 1989;10:437–44.
8. Maseri A. Angina pectoris: expanded concepts. Adv Intern Med 1987;32:27–68.
9. Krauss KR, Hutter AM, de Sanctis RW. Acute coronary insufficiency. Course and follow up. Arch Intern Med 1972;129: 808–13.
10. Gazes PC, Mobley EM Jr, Faris HM Jr, Duncan RC, Humphries GB. Preinfarctional (unstable) angina—a prospective study—ten year follow-up. Circulation 1973:48:331–7.
11. Otton PE, Wilson EJ. The cardiocirculatory effects of upper thoracic epidural analgesia. Can Anaesth Soc J 1966;13:541–9.
12. McLean APH, Mulligan GW, Otton P, MacLean LD. Hemodynamic alterations associated with epidural anesthesia. Surgery 1967;62:79–87.
13. Wattwil M, Sundberg A, Arvill A, Lennquist C. Circulatory changes during high thoracic epidural anaesthesia—influence of sympathetic block and of systemic effect of the local anaesthetic. Acta Anaesthesiol Scand 1985;29:849–55.
14. Feigl EO. Coronary physiology. Physiol Rev 1983;63:1–205.
15. Maseri A. Role of coronary artery spasm in symptomatic and silent myocardial ischemia. J Am Coll Cardiol 1987;9:249–62.
16. Shepherd JT, Vanhoutte PM. Spasm of the coronary arteries causes and consequences (the scientist's viewpoint). Mayo Clin Proc 1985;60:33–46.
17. Reiz S, Nath S, Rais O. Effects of thoracic epidural block and prenalterol on coronary vascular resistance and myocardial metabolism in patients with coronary artery disease. Acta Anaesthesiol Scand 1980;24:11–6.
18. Marcus ML. Autoregulation in the coronary circulation. The coronary circulation in health and disease. New York: McGraw-Hill, 1983:93–112.

ANESTH ANALG 56
1989;69:563–9

Acute Toxicity of Ropivacaine Compared with That of Bupivacaine

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SCOTT DB, LEE A, FAGAN D, BOWLER GMR, BLOOMFIELD P, LUNDH R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 1989;69:563–9.

The acute central nervous and cardiovascular effects of the local anesthetics ropivacaine and bupivacaine were compared in 12 volunteers in a randomized double-blind manner with use of intravenous infusions at a rate of 10 mg/min up to a maximal dose of 150 mg. The volunteers were all healthy men. They were familiarized with the central nervous system (CNS) toxic effects of local anesthetics by receiving a preliminary intravenous injection of lidocaine. The infusions of ropivacaine and bupivacaine were given not <7 days apart.

CNS toxicity was identified by the CNS symptoms and the volunteers were told to request that the infusion be stopped when they felt definite but not severe symptoms of toxicity such as numbness of the mouth, lightheadedness, and tinnitus. In the absence of definite symptoms, the infusion was stopped after 150 mg had been given.

Cardiovascular system (CVS) changes in conductivity and myocardial contractility were monitored using an interpretive electrocardiograph (which measured PR interval, QRS duration, and QT interval corrected for heart rate) and echocardiography (which measured left ventricular dimensions from which stroke volume and ejection fraction were calculated).

Ropivacaine caused less CNS symptoms and was at least 25% less toxic than bupivacaine in regard to the dose tolerated. Both drugs increased heart rate and arterial pressure. Stroke volume and ejection fraction were reduced. There was no change in cardiac output. Although both drugs caused evidence of depression of conductivity and contractility, these appeared at lower dosage and lower plasma concentrations with bupivacaine than with ropivacaine.

Ropivacaine is a less toxic compound than bupivacaine, but their relative therapeutic ratios must await the results of clinical trials in humans to assess the potency of ropivacaine compared with that of bupivacaine.

Key Words: ANESTHETICS, LOCAL—ropivacaine, bupivacaine. TOXICITY, LOCAL ANESTHETICS.

Ropivacaine is the (S)-enantiomer of 1-propyl-2′,6′-pipecoloxylidide, an amide local anesthetic with a structure similar to that of mepivacaine and bupivacaine. Animal studies (1–3) have indicated that ropivacaine is less toxic than bupivacaine. Both drugs have a comparatively long duration of action, but their relative potency has still to be determined in humans.

As virtually all local anesthetics produce a similar profile of symptoms and signs related to that of the central nervous system (CNS), it is relatively easy to compare them in volunteers in a randomized double-blind manner (4).

Cardiovascular toxicity is less easy to study, as clinical signs are not usually seen until the CNS toxicity is marked and well beyond that which tolerable to either a volunteer or a patient. Howeve the detection of asymptomatic changes in cardi conduction and contractility has been made easi with modern noninvasive technology, and this can used to determine whether objective signs of chang in conductivity and contractility can be detecte when only mild CNS toxicity is present.

As ropivacaine is a long acting local anesthetic, should have a clinical profile similar to that of bupi acaine and a knowledge of their respective system toxicity in humans is of importance. To compare t acute toxicity of ropivacaine and bupivacaine on bo the CNS and the cardiovascular system (CVS), t following study was undertaken.

Methods

Ethical permission for the study was obtained fro the Lothian Health Board ethical committee. Twel

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healthy male volunteers took part. After a full medical examination including routine electrocardiography (ECG), biochemistry, and hematology, they were acquainted with the mild toxic effects of local anesthetics by receiving IV lidocaine given at a rate of 100 mg/min until the volunteer was aware of the early symptoms of toxicity (lightheadedness, tinnitus, numbness of the tongue). As soon as the subject was aware of definite symptoms, the injection was stopped. The dose producing such symptoms was 80–200 mg.

At the preliminary medical examination, each subject also underwent echocardiography. As it is not possible to obtain high grade echorecordings from every person, we wished to identify those who would be suitable for this particular method. In the event, 8 of the 12 proved suitable and echocardiography (vide infra) was performed on them during their two drug infusions.

Infusion. The study proper in each individual started several days after the IV lidocaine. No other drugs were taken in the week before the study and no alcohol or tobacco was consumed in the 24 h before the study. Each volunteer received two infusions, one of 0.5% bupivacaine HCl and one of 0.5% ropivacaine HCl (as aqueous solutions), at least 7 days apart and in a randomized order. The infusion rate was 10 mg/min (2 mL/min) with use of a Harvard infusion pump. The infusion was stopped at the request of the volunteer when he experienced definite CNS symptoms. If no symptoms occurred or were only of a minor degree, the infusion was stopped after 150 mg had been injected.

Monitoring. Symptoms of CNS toxicity were reported as and when they occurred, in response to frequent direct questioning, and were graded for severity on a 0–4 scale by the volunteer. Though the grades were recorded, they were used to assess the progress of toxicity in regard to time during the infusion and were not subjected to subsequent analysis.

The ECG was displayed continuously on a Roche 125 monitor and recorded continuously with a Medilog tape recorder. A 12-lead ECG was recorded before and every 5 min during the infusion. A recording was also taken at the end of the infusion, and every 5 min thereafter for 30 min. A Hewlett-Packard Pagewriter Interpretive Cardiograph was used for this purpose. This instrument calculates the PR interval, QRS duration, QT interval, QT interval corrected for heart rate, and QRS axis.

A Dynamap 845 was used to measure and record systolic and diastolic blood pressures, together with heart rate, at 2-min intervals throughout. Echocardiography was performed on 8 of the 12 subjects (vide supra) with use of an Ekoline 21 SKI M-mode machine. The eight subjects were placed on a specially made table on which they were horizontal with up to a 30° tilt to the left, the final position chosen being that which gave a clear echorecording. The echocardiograph machine was connected to an Ekoline 21 ultraviolet strip chart recorder on which the V5 ECG waveform was simultaneously recorded with the echocardiograph. A 2.25-MHz 13-mm-diameter piezoelectric ultrasound transducer was used. The chart speed was 50 mm/sec with tissue depth markers at 1-cm intervals and time markers at 0.5-sec intervals. Calibration was performed before the investigations by the hospital Department of Medical Physics and Medical Engineering. The transducer was placed either at the third or the fourth left parasternal intercostal space, whichever enabled the transducer to be closest to right angles to the body surface in all planes when recordings were made at the level of the anterior mitral valve leaflet (5). The positions of the subject and the transducer were the same for both infusions. After recording, the charts were marked out in preparation for digitization by one of us (GMRB) and checked by another (FB) before digitizing on a dedicated echocardiographic analysis system (Cardio-80, Kontron). Both observers were blinded to the identity of the drug infused.

The methodology used to determine the left ventricular dimensions followed the recommendations of the Committee on M-mode Standardization of the American Society of Echocardiography (6) and a standard textbook (7). The leading edge method (most anterior edge of endocardial lines) was always used and all measurements quoted were the mean of three cardiac cycles. End-diastolic diameter (EDD) was timed at the onset of the first deflection of the QRS complex on the simultaneously recorded ECG. End-systolic diameter (ESD) was timed from the peak of the motion of the posterior wall of the left ventricle. Heart rate (HR) was derived from the RR interval on the ECG over three cycles. The left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated by the program using the Teicholz formula (8): Stroke volume (SV) = EDV − ESV; Cardiac output (CO) = SV × HR. Shortening fraction (SF) was calculated from the formula SF = (EDD − ESD)/EDD × 100%. Ejection fraction (EF) was calculated from the formula EF = (EDV − ESV)/EDV × 100%.

Blood sampling. Five-milliliter samples of venous blood from the arm contralateral to that used for the

Table 1. Demographic Data of 12 Subjects Receiving Both Ropivacaine and Bupivacaine

Subject	Age (years)	Height (cm)	Weight (kg)
1	26	175	68
2	34	183	81
3*	20	183	66
4*	27	186	83
5*	30	173	69
6*	30	173	67
7*	31	172	58
8	26	186	69
9	21	167	75
10*	30	178	73
11*	32	175	77
12*	28	183	83
Mean	28	178	72
Range	20–34	167–186	58–83

*Indicates those subjects who underwent echocardiography.

Table 2. Individual and Mean IV Doses of Ropivacaine and Bupivacaine Tolerated in 12 Subjects

Subject	Tolerated IV dose (mg)	
	Ropivacaine	Bupivacai
1	150	150
2	150	120
3	67	65
4	65	75
5	150	95
6	62	60
7	150	85
8	150	133
9	150	105
10	137	82
11	150	138
12	110	75
Mean ± SD	124 ± 38	99 ± 3
	$P < 0.01$	

infusion were taken before the infusion was started, at the time of reporting the first symptoms, at the end of the infusion, and every 5 min thereafter until 10 min after the disappearance of all symptoms. The plasma was separated and frozen at −20°C before analysis. The concentration of ropivacaine in the plasma was determined by gas chromatography with use of nitrogen sensitive detection at the Astra Bioanalytical Laboratories, Södertalje, Sweden.

Data analysis. Wilcoxon signed rank tests were used to compare the between treatment data (bupivacaine versus ropivacaine) and also the within treatment data (control values versus data during and after infusion with each drug). As the measured variables differed in regard to sampling time due to the difference in time to first symptoms, the measurements have been identified as C = control data (preinfusion); F = data at first symptoms; E = end of infusion; E + X = end of infusion + x min. The null hypothesis was rejected at the $P < 0.05$ level.

Results

The demographic data of the 12 subjects are shown in Table 1.

Dose of drug. Seven subjects tolerated the full 150-mg dose of ropivacaine, but only one tolerated the same dose of bupivacaine. The individual doses are shown in Table 2. The mean dosage of ropivacaine was 124 mg and of bupivacaine 99 mg. This difference was statistically significant ($P < 0.01$).

Symptoms. The onset of symptoms from the start of the infusion was on average 4 min with bupivacaine and 6 min with ropivacaine ($P < 0.02$). The time maximal effect was 10 min with bupivacaine and min with ropivacaine ($P < 0.05$). The duration symptoms (17 min with bupivacaine and 15 min wi ropivacaine) did not differ significantly. The sym toms were those expected from local anesthetic dru and similar to those during the preliminary lidocai injection. The severity and frequency of sympto were greater with bupivacaine, only one subje tolerating the maximal dose (150 mg) compared wi 7 with ropivacaine.

Plasma concentrations. Although there were indivi ual variations, the majority of the symptoms occurr at plasma concentrations of either drug between and 2 μg/mL. The mean plasma concentrations of t two drugs at the appearance of symptoms (F), at t end of infusion (E), and 5 min (E + 5) and 30 min + 30) after the infusion are shown in Figure 1. T concentrations of ropivacaine were greater than tho of bupivacaine at all sample times, these being si nificantly different ($P < 0.05$) at E and E + 5. By t end of the infusion, on average 25% more ropivacai had been given than bupivacaine.

Cardiovascular changes. The mean data for arter pressure and heart rate for all 12 subjects are sho in Figures 2a and 2b. Both drugs were associated wi small increases in both pressure and heart rate, whi were statistically significantly different from cont values ($P < 0.01$) except for the change in he rate with ropivacaine which was not statistical significant. There were no differences between t drugs.

The mean data for PR interval, QRS duration, a QT interval (corrected for heart rate) are shown

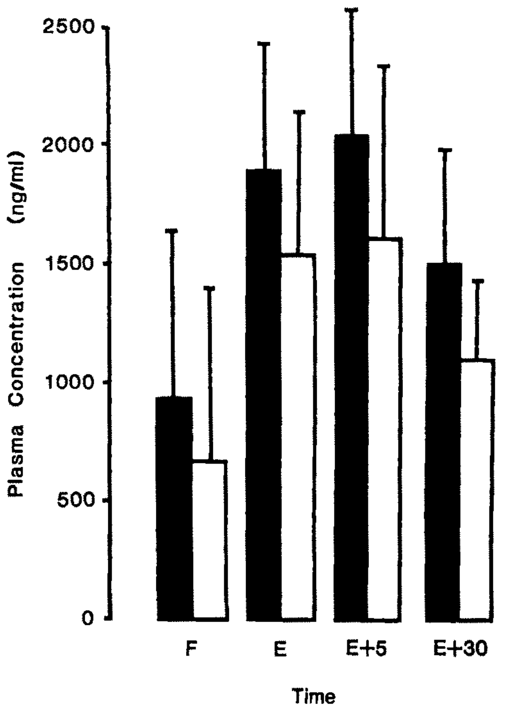

Figure 1. Mean plasma concentrations of ropivacaine (solid bar) and bupivacaine (open bar) at the following sample times: appearance of first CNS symptoms (F), end of infusion (E), and 5 min (E + 5) and 30 min (E + 30) after the infusion. There was a statistically significant difference ($P < 0.05$) between drugs at E and E + 5. Vertical lines represent 1 SD.

Figures 3a, 3b, and 3c. Bupivacaine significantly increased all three, both at the end of infusion (E) and 5 min later (E + 5). Ropivacaine significantly increased the PR interval only at E + 5. The only statistical difference between the drugs was in regard to the QRS duration at E + 5.

No cardiac arrhythmias were detected during the infusions or on replay of the Medilog tapes. The echocardiographic data obtained with ropivacaine and bupivacaine in the eight subjects in which this investigation was carried out are shown in Table 3. The mean control values, and those obtained at the end of infusion when CNS toxicity was maximal, are shown. Neither drug caused a significant change in EDD, but the ESD was increased with both drugs, though statistical significance was only reached with ropivacaine. Therefore, SV decreased significantly with both drugs as did SF and EF. Heart rate increased significantly with both drugs (as opposed to all 12 subjects). There was consequently no change in calculated cardiac output. Both systolic and diastolic blood pressures in these eight subjects increased significantly with both drugs. The mean plasma concentration of bupivacaine in the eight echocardiograph subjects was 1.22 μg/mL, which was 38% lower than that of ropivacaine, 1.70 μg/mL ($P < 0.05$). The respective mean doses in the eight subjects were 81 mg for bupivacaine and 108 mg for ropivacaine.

Discussion

There was a clear difference between the drugs in regard to their ability to produce mild symptoms of CNS toxicity. The 12 subjects tolerated 25% more ropivacaine than bupivacaine. This result almost certainly underestimates the difference between the drugs, because on seven occasions, the maximal dose allowed by the protocol (150 mg) was reached with ropivacaine compared with only one occasion with bupivacaine. The CNS symptoms were similar to those experienced in previous studies (9), and no unexpected side effects were noted.

The plasma concentrations measured were unremarkable and consistent with the pharmacokinetic data previously determined for the two drugs (10,11). The apparent paradox that the peripheral venous concentrations of both drugs were greater in most subjects 5 min after the infusion ended (E + 5) than when the infusions were stopped (E), is most probably because arterial and venous plasma concentrations had not reached equilibrium at E. The arterial concentrations would be highest at or very soon after the end of the infusion and greater than the venous concentration. Because drug was still being taken up by the tissues of the upper limb, it would take some minutes for the venous concentration to equalize with the arterial concentration. The use of peripheral venous plasma concentrations during rapid high dose IV infusions is fraught with problems, particularly when they are to be related to CNS changes (12). However, the use of arterial samples, which would be more informative, was not considered appropriate for the present volunteer study.

In spite of these reservations, it is reasonable to suggest that symptoms of CNS toxicity occur at lower plasma concentrations with bupivacaine than is the case with ropivacaine. There was a 40% difference between the mean plasma concentrations of the two drugs at the time symptoms first appeared (F). At the peak concentrations after stopping the infusions, ropivacaine concentrations were on average 27% higher than those of bupivacaine, in spite of the subjects having considerably less severe symptoms. The consistent increases in heart rates and arterial pressures during the infusions have been noted previously with local anesthetics (8). Although these increases might be explained by anxiety, it seems to be so reproducible that one must accept it as a

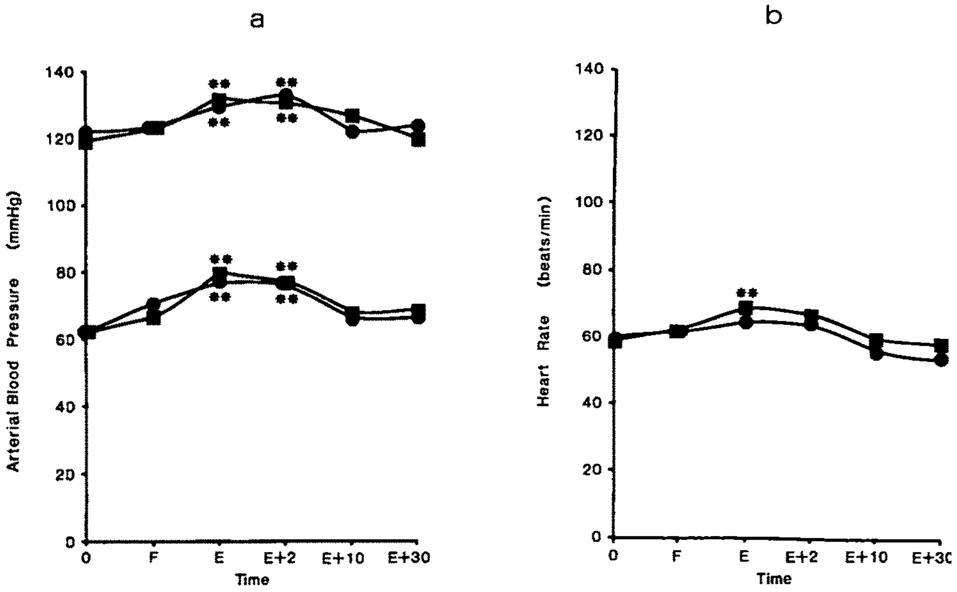

Figure 2. a) Mean systolic and diastolic arterial pressures, and b) mean heart rates before, during, and after the infusion of ropivacaine and bupivacaine. 0 = control values, F = first symptoms, E = end of infusion, E + 2, E + 10, and E + 30 = 2, 10, and 30 min after end of infusion. **Indicates statistically significant difference, $P < 0.01$, compared with control value. ● = ropivacaine, ■ = bupivacaine.

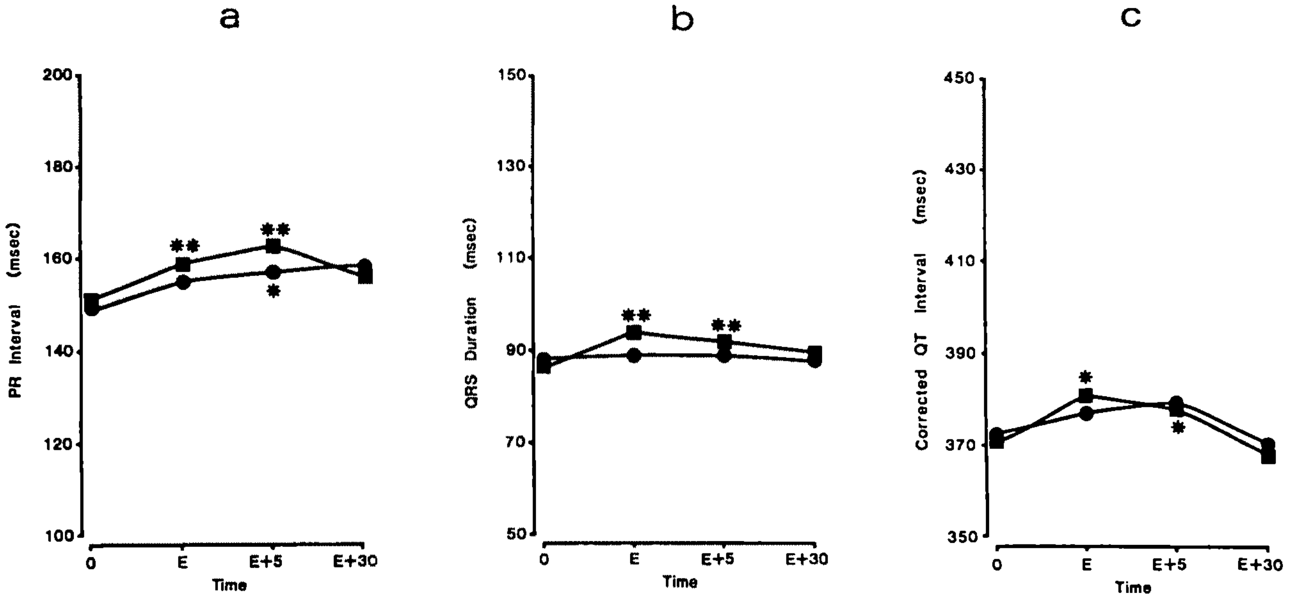

Figure 3. a) Mean PR intervals, b) mean QRS duration, and c) mean QT intervals (corrected for heart rate) before, during, and after infusion of ropivacaine or bupivacaine. 0 = control values, F = first symptoms, E = end of infusion, E + 2, E + 10, and E + 30 = 2, 10, and 30 min after end of infusion. **Indicates statistically significant ($P < 0.01$) change from control; *indicates $P < 0.05$. The drugs only differed significantly, $P < 0.05$, in regard to QRS duration at E + 5. ● = ropivacaine, ■ = bupivacaine.

pharmacodynamic effect of amide local anesthetic drugs.

The interpretive ECG used in this study greatly assisted the analysis of changes in cardiac conduction and was able to detect small but real increases in PR interval, QRS duration, and QT interval corrected for heart rate. Local anesthetic drugs are known to cause changes in both conductivity and contractility of the myocardium (13), although clinical evidence of the latter is usually only apparent with very high plasma concentrations, considerably greater than those which cause convulsions. A major cause of death with bupivacaine appears to be ventricular fibrillation (14,15). The present study has shown that effects on both conductivity and contractility can be detected at much lower plasma concentrations when more sensitive methods are used. Echocardiography is especially useful as it is noninvasive. Although M-mode echocardiography has been largely replaced by two-dimensional machines in the diagnostic field, it is an

P 24,558

Table 3. Cardiovascular Variables (mean ± SD) and Mean Plasma Concentrations in Eight Subjects Undergoing Echocardiography Before and at the End of IV Infusion

	Ropivacaine			Bupivacaine			Ropivacaine vs. bupivacaine (*P*)
	Control	End of infusion	Control vs. end infusion (*P*)	Control	End of infusion	Control vs. end infusion (*P*)	
EDD (cm)	5.2 ± 0.4	5.1 ± 0.4	NS	5.1 ± 0.2	5.0 ± 0.4	NS	NS
ESD (cm)	3.4 ± 0.2	3.7 ± 0.4	0.05	3.2 ± 0.2	3.5 ± 0.5	NS	NS
SV (mL)	80.8 ± 19.5	68.9 ± 14.8	0.05	80.8 ± 13.6	67.4 ± 19.2	0.05	NS
SF (%)	34.4 ± 4.4	28.7 ± 5.8	0.05	36.5 ± 4.5	29.7 ± 8.3	0.05	NS
EF (%)	62.9 ± 6.0	54.6 ± 8.5	0.05	65.8 ± 5.9	55.7 ± 12.6	0.05	NS
HR (beats/min)	52.8 ± 7.2	63.1 ± 10.0	0.05	54.8 ± 10.3	60.4 ± 10.3	0.05	NS
CO (L/min)	4.3 ± 1.1	4.4 ± 1.1	NS	4.4 ± 0.7	4.0 ± 1.0	NS	NS
SAP (mm Hg)	121.9 ± 16.0	128.9 ± 14.0	0.05	118.0 ± 8.5	127.1 ± 8.5	0.05	NS
DAP (mm Hg)	65.1 ± 9.9	78.7 ± 8.7	0.05	60.6 ± 6.6	78.9 ± 10.1	0.05	NS
Plasma concentration (μg/mL)	—	1.70 ± 0.54	—	—	1.22 ± 0.42	—	0.05

CO = cardiac output; DAP = diastolic arterial pressure; EDD = end-diastolic diameter; EF = ejection fraction; ESD = end-systolic diameter; HR = heart rate; NS, not significant; SAP = systolic arterial pressure; SF = shortening fraction; SV = stroke volume.

accurate method for determining the dynamic changes in a normal heart (7,16,17). EF and SV were reduced though the increase in heart rate kept the cardiac output unchanged. All the variables that showed significant changes nevertheless remained within normal limits.

Such changes as did occur were associated with lower plasma concentrations of bupivacaine than was the case with ropivacaine. At the time of stopping the infusions, the venous plasma concentration of bupivacaine was 38% less than that of ropivacaine. Changes in the echocardiograph similar to those seen in the present study have been described with disopyramide, but not with lidocaine at a plasma concentration of 4 μg/mL (18). Obvious clinical signs of CVS changes due to local anesthetic drugs occur at plasma concentrations considerably greater than those which cause CNS symptoms and signs. However, it is now possible to detect CVS changes before clinical signs develop. We believe this work is the first study in humans to show changes in both conductivity and contractility of the myocardium at plasma concentrations of local anesthetic that only cause minor symptoms of CNS toxicity.

Ropivacaine is a less toxic drug than bupivacaine in regard to the production of mild CNS and CVS toxicity by intravenous infusion. Whether ropivacaine has a greater therapeutic ratio than that of bupivacaine can only be determined by clinical trials designed to elucidate the relative local anesthetic potency of the two drugs. Although there are published data (19) on relative potency in the rat and the dog, animal studies should only be accepted as rough guides to the situation in humans. For example, Feldman and Covino (19) found considerable species difference between the rat and the dog and were only able to assess motor blockade. The significance of the difference in systemic toxicity shown in the present study cannot be assessed until reliable clinical data are available.

References

1. Akerman B, Hellberg I-B, Trossvik C. Primary evaluation of the local anesthetic properties of the amino amide agent ropivacaine (LEA 103). Acta Anaesthesiol Scand 1988;32:571–8.
2. Arthur GR, Feldman HS, Norway SB, Doucette AM, Covino BG. Acute iv toxicity of LEA-103, a new local anesthetic, compared to lidocaine and bupivacaine in the awake dog. Anesthesiology 1986;65:A182.
3. Reiz S, Nath S. Cardiotoxicity of LEA 103—a new amide local anesthetic agent. Anesthesiology 1986;65:A221.
4. Scott DB. Toxic effects of local anaesthetic agents on the central nervous system. Br J Anaesth 1986;58:732–5.
5. Popp RL, Filly K, Brown OR, Harrison DC. Effect of transducer placement on echocardiographic measurement of left ventricular dimensions. Am J Cardiol 1975;35:537–40.
6. Sahn DJ, DeMaria A, Kisslo J, Weymann A. The committee on M-mode standardization of the American Society of Echocardiography: recommendations regarding quantitation in M-mode echocardiography: results of a survey in echocardiographic measurements. Circulation 1978;58:1072–83.
7. Folland ED, Parisi AF. Assessment of left ventricular function. In: Morganroth J, Parisi AF, Pohost GM, eds. Echocardiography, noninvasive cardiac imaging. Chicago: Year Book Medical Publishers, 1983:55–70.
8. Teicholz LE, Cohen MV, Sonnenblick EH, Gorlin R. Study of left ventricular geometry and function by B scan ultrasonography in patients with and without asynergy. N Engl J Med 1974;291:1220–6.
9. Scott DB. Evaluation of the toxicity of local anaesthetic agents in man. Br J Anaesth 1975;47:56–9.

10. Tucker GT, Mather LE. Clinical pharmacokinetics of local anaesthetic agents. Clin Pharmacokinet 1979;4:241–6.
11. Lee A, Fagan D, Scott DB, Tucker GT. Pharmacokinetics of ropivacaine in man. Anesth Analg (in press).
12. Tucker GT. Pharmacokinetics of local anaesthetics. Br J Anaesth 1986;58:717–31.
13. Reiz S, Nath S. Cardiotoxicity of local anaesthetic agents. Br J Anaesth 1986;58:736–46.
14. Albright EA. Cardiac arrest following regional anesthesia with etidocaine and bupivacaine. Anesthesiology 1979;51:285–7.
15. Cardiotoxicity of local anaesthetic drugs (editorial). Lancet 1986;2:1182–94.
16. Martin MA, Fieller NRJ. Echocardiography in cardiovascular drug assessment. Br Heart J 1979;41:536–43.
17. Martin MA. Assessment of correction formula for echocardiographic estimations of left ventricular volumes. Br Heart J 1978;40:294–6.
18. Martin MA, Bax NDS, Tucker GT, Ward JW. Disopyramide and lignocaine. A comparison of effects using echocardiography. Br J Clin Pharmacol 1980;10:237–44.
19. Feldman HS, Covino BG. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. Anesth Analg 1988;67:1047–52.

Growth of Allogeneic Sarcoma in Mice Subjected to Halothane Anesthesia and/or Surgical Stress

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RADOŠEVIĆ-STAŠIĆ B, UDOVIĆ-ŠIROLA M, STOJANOV L, RIBARIĆ L, RUKAVINA D. Growth of allogeneic sarcoma in mice subjected to halothane anesthesia and/or surgical stress. Anesth Analg 1989;69:570–4.

The present study was designed to clarify mechanisms involved in suppression of cell-mediated immunity reported in patients undergoing major surgery with general anesthesia by determining the effects of halothane anesthesia with and without surgery on the growth of Sarcoma I (Sa I), a tumor allogeneic to BALB/c mice. Mice were given subcutaneous injections of 5×10^6 tumor cells from A/Jax mice and then immediately exposed to 0.5%–1.0% halothane for 1 hr without surgery ($n = 7$) or with surgery (midline laparotomy; $n = 12$). In control groups mice were also injected with tumor cells but were not exposed to prolonged halothane anesthesia. Some of them received only Sa I ($n = 6$), while the rest ($n = 7$) were also laparctomized. The rejection time of Sa I in mice exposed to halothane anesthesia was significantly longer (15.4 ± 1.25 days) than in untreated controls (12.0 ± 0.68 days) ($P < 0.05$). In the mice exposed to halothane tumor growth was also greater. Surgical stress per se did not significantly affect growth or rejection time of Sa I (11.0 ± 0.66 vs 12.0 ± 0.68 days). Similarly, the combination of surgical stress with halothane anesthesia did not affect the immunosuppression associated with halothane alone (12.9 ± 1.3 vs 15.4 ± 1.25; $P < 0.05$). The results indicate that halothane anesthesia per se may be associated with impairment of cell-mediated immunity under experimental conditions.

Key Words: ANESTHETICS, VOLATILE—halothane. IMMUNE RESPONSE, HALOTHANE. CANCER, HALOTHANE.

It has been suggested that the transient immunodepression that develops after general anesthesia and surgery may contribute to the propagation of infection, impairment of wound healing, and spread or growth of malignancies (1–3). This may reflect the effects of the anesthetics and/or concomitant operative stress on immune response. There is, however, a lack of agreement about the mechanism by which anesthesia and/or surgery may affect host immunocompetence. In our previous study we observed that immunosuppression in postoperative patients is greater after general than after epidural anesthesia. This pointed to direct effects of halothane or to some participation of stress-induced mechanisms in the observed immunosuppression, since it could be presumed that adrenal stimulation was less with epidural anesthesia because of the blockade of preganglionic sympathetic fibers. In order to obtain more information on mechanisms involved in the development of immunodepression, we attempted in this study to compare the effects of halothane anesthesia alone with the effects of the combination of anesthesia and operation, using as an index of changes of cellular immunity growth and rejection time of Sarcoma I (Sa I), a tumor from A/Jax mice which is allogeneic to the BALB/c mice we used as recipients.

Material and Methods

All experiments were done in male BALB/c (H-2^d) mice, aged 2.5–3.5 months. These were inoculated with Sa I tumor cells obtained from ascitic fluid of tumor-bearing A/Jax (H-2^a) mice. A cell suspension was prepared by diluting tumor cells in Hank's

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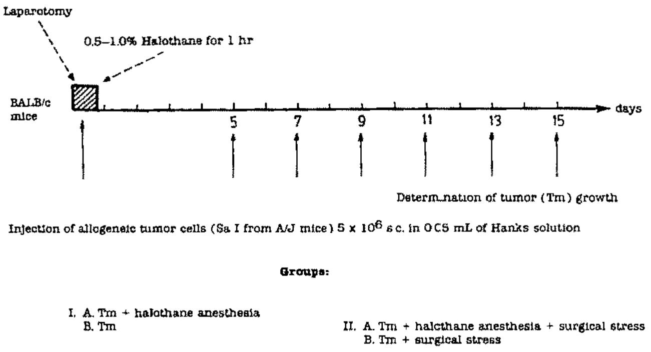
Laparotomy
0.5–1.0% Halothane for 1 hr
BALB/c mice
days
5
7
9
11
13
15
Determ.nation of tumor (Tm) growth
Injection of allogeneic tumor cells (Sa I from A/J mice) 5 x 10^6 s.c. in 0.C5 mL of Hanks solution
Groups:
I. A. Tm + halothane anesthesia
B. Tm
II. A. Tm + halcthane anesthesia + surgical stress
B. Tm + surgical stress

Figure 1. Experimental protocol for the determination of growth and rejection times of an allogeneic tumor in mice

balanced salt solution (HBSS). The viability of cells was always greater than 90%, as determined by exclusion of trypan blue dye. An inoculum of 5 × 10^6 tumor cells in 0.05 mL of HBSS was injected subcutaneously in the right hind leg of all our mice, after which the animals were divided into two main groups—I and II, which were further subdivided into experimental (A) and control (B) groups (Figure 1). In group IA the effect of halothane alone was studied, while in group IIA the combination of the effects of halothane anesthesia and operation were analyzed.

Anesthetization of mice was performed in a 1-L animal metabolic cage containing soda lime for carbon dioxide absorption. The air with or without halothane (which came from a Fluotec vaporizer) was added to the chamber by the use of a respirator for small animals adjusted for a total flow of 0.4 L/min. Anesthesia with 0.5%–1.0% halothane started immediately after the inoculation of tumor cells (group IA = Tm + halothane), or immediately after the surgery (group IIA = Tm + surgical stress + halothane) and continued for 1 hr. Mice in the control (B) groups were treated identically as those in group A. They were put in the same metabolic cage for 1 hr, but without halothane in the air added to the chamber (IB = only tumor; IIB = Tm + surgical stress). The nonspecific surgical stress consisted of a midline laparotomy. It was performed in all animals in groups IIA and IIB under short (3 min) halothane anesthesia. In group IIA the anesthesia was then administered for another hour; it was immediately discontinued in group IIB. In all mice, tumor growth was determined on the basis of the frequency and time of Sa I rejection, which was estimated for the mean diameter of subcutaneous nodules of the tumor and times of their disappearance (rejection times). The incidence of reappearance of tumor after its regression and death of animals was also recorded.

Statistical analysis was performed by Student's *t*-test and χ^2 assay. Values of $P < 0.05$ were consi ered statistically significant.

Results

Only three out of the 32 animals inoculated with S cells failed to develop tumors, and all except one these 29 mice that accepted allogeneic tumor we able to reject it. The number of these exceptions (n 4) was too small to be of statistical significance (ble 1).

Statistically relevant differences were, howev found when mean rejection times were compar between the groups (Table 1). Mice given halotha without operation (group IA) tolerated tumors long than did mice without halothane (group IB) (*P* 0.05), suggesting that halothane alone has a suppr sive effect on cell-mediated immunity. This conc sion is also supported by the fact that in the sa group (IA) the mean tumor diameter was the great and that one mouse died after the reappearance sarcoma at the site of inoculation. Although the observations were not statistically significant, it interesting that they were seen in group A on Surgical stress provoked by laparotomy did n change the times of the rejection of Sa I (groups IIB IB), but the "stress" of laparotomy associated wit hr of halothane anesthesia resulted in some impa ment of immunosuppression provoked by t halothane anesthesia alone (groups IIA vs IA). I creases in the size and rejection times of tumors se in group IIA were, however, not statistically sign cant, in comparison with values found in group I

The results, therefore, point to the immunosu pressive effect of halothane alone (group IA) and the lack of a synergistic effect of halothane anesthe and laparotomy, used as a stress event, on ce mediated immune response.

Discussion

Despite the large body of evidence that points to t immunosuppressive properties of both halothane a esthesia and surgical stress (1–3), comparisons b tween the effects of these two conditions in the sa experimental model are infrequent. Humphrey al. (5) compared the effects of exposure to 0. halothane for 1 hr to those obtained after amputati of one hind limb on the humoral immune response rats. The data showed that both procedures inhi the generation of antibody-producing cells in sple to sheep red blood cells (SRBC) given 6–7 days bef

Table 1. Growth of Allogeneic Tumor in BALB/c Mice Subjected to Separate or Combined Effects of Halothane Anesthesia and Surgical Stress

Group	Treatment	No. of mice	No. of accepted tumors	Maximal diameter (mm)	Rejection time (days)	Reappearance of Sa I	Death of animals (No.)
I.	A. Tm + halothane	7	6/7	7.36 ± 1.05	15.43 ± 1.25*	1/7	1/7
	B. Tm	6	6/6	6.33 ± 0.73	12.0 ± 0.68	0/6	0/6
II.	A. Tm + operation + halothane	12	10/12	5.0 ± 0.57	12.9 ± 1.3	0/12	0/12
	B. Tm + operation	7	7/7	5.8 ± 0.63	11.0 ± 0.66	0/7	0/7

Tm = Sarcoma I (Sa I) injected subcutaneously immediately before halothane anesthesia (0.5%–1.0% for 1 hr); Operation = midline laparotomy done immediately after the inoculation of Sa I.

Results are expressed as mean ± standard error.

*A statistically significant difference was found only between groups IA and IB ($P < 0.05$).

amputation or exposure to halothane. The observed depression was of similar degree and lasted 48 hr. In a slightly different model we noticed that even shorter exposures of mice to halothane (1 hr after the challenge with SRBC) induce significant suppression of plaque-forming cells generation. Surgical stress which consisted of a midline laparotomy potentiated this immunosuppression, indicating that additional inhibitory pathways were probably activated (6).

Data presented in this study show that halothane anesthesia alone also inhibits the cell-mediated immune reactions responsible for the rejection of allogeneic tumors. Our results, however, differ from those obtained by Cullen and Sundsmo (7) with the same allogeneic tumor but under different experimental conditions. In $C_{57}Bl/_6$ (H-2^b) mice as recipients, they noticed that anesthesia with 0.5%–0.7% halothane, administered for 5 hr on the day of tumor inoculation and 1 week later, did not influence the time of tumor appearance, rate of tumor growth, or time of tumor regression. The observed difference in results could be caused by reexposure to halothane, which may eliminate and cancel the inhibitory effect of the first exposure to halothane. However, the results of Cullen and Sundsmo (7) demonstrate that such inhibition of immunoresponse to allogeneic tumors does not exist even in the early period of tumor growth. It is therefore likely that BALB/c (H-2^d) mice, which we used in our experiments, are more sensitive to the action of halothane. It should also be emphasized that the dynamics of tumor growth in our study differed from that of Cullen and Sundsmo even in the control, unanesthetized mice, with tumor regression times of 20.3 ± 5.5 days reported by Cullen and Sundsmo (7) and 12.0 ± 0.68 days in our present experiments (group IB).

Immunosuppression in our study was a consequence of the relatively short exposure of BALB/c mice to halothane (for only 1 hr after the implantation of tumor cells). It is therefore likely that halothane anesthesia particularly affects the early postimplantation events, when the process of tumor recognition occurs. A/Jax-derived Sa I (H-2^a) is a tumor which expresses K^k, D^d, and L^d antigens but is devoid of class II Ia molecules on the cell surface, as determined by flow cytometric analysis (8). Grafts that differ from the recipient only at class I regions of major histocompatibility complex (MHC) may be rejected by two potential pathways (9,10): (1) through the activation of Lyt 2^+ T cells (which express cytolytic activity after direct class I antigen recognition); and (2) by the action of $L_3T_4^+$ T (helper) cells which may recognize class I alloantigen in association with self Ia structures. The latter form of T-cell activation may involve processing and presentation of alloantigens on host antigen-presenting cells (APC) or corecognition of class I alloantigen and syngeneic Ia molecules on donor APC (11,12). The primary pathway for the rejection of Sa I tumor in BALB/c mice has been reported (13) to be the direct activation of class I-MHC antigen-reactive Lyt 2^+ T cells, because it has been found that in vivo depletion of the $L_3T_4^+$ T-cell subset does not prolong Sa I tumor growth, in contrast to the induction of lethal tumor growth of recipient mice in which the Lyt-2^+ subset had been depleted (13). $L_3T_4^+$ T cells may, however, on one hand augment the Lyt 2^+ T-cell response to Sa I (13) and on the other facilitate the response of B lymphocytes in the production of antitumor antibodies, which may promote progressive tumor growth by the production of an immunologic enhancement (14). From this it is apparent that multiple factors and cells are involved in the immune response to Sa I. Halothane may affect all or almost all of them. It is known that halothane anesthesia may inhibit the process of phagocytosis (15,16), mobility of lymphocytes (17), lymphocyte transformation and division (18), and also the process of the killing of tumor cells by peritoneal exudate cells (19). During the early postoperative period, the generation of cytotoxic T cells is also depressed, because of the presence of suppressor macrophages (20). It has been reported that antibody-dependent cellular cytotoxicity of patients' lymphocytes against coated tumor cells decreases after minor surgery and anesthesia (21). This suggests that the prolonged time of tumor rejection in our study may be related also to changes in the activity of NK or K cells after exposure to halothane. Although it is reported that suppression of NK-cell cytotoxicity (NKCC) is mainly related to the effects of surgical stress (20,22,23), it has been shown that even short periods of anesthesia with pentobarbital may result in an early decrease in NKCC (23). An additional support for the immunosuppressive properties of halothane came from data showing that exposure of fibrosarcoma-bearing mice to 1.5% halothane for 1.5 hr may activate the suppression of the cell-mediated immunity of tumor-bearing animals (24).

Halothane may also have direct toxic effects (25) on several cells participating in the immune response to Sa I. At the same time halothane anesthesia produces homeostatic changes, with a disarrangement of many of the feedback pathways that exist between the neuroendocrine and immune systems (26). Halothane may apparently affect both the afferent and the efferent limbs of these loops. Because of the suppressive action of halothane on mononuclear phagocytes, it can be presumed that the production of interleukin-1 (IL-1) is also depressed. Recent evidence (27) shows that IL-1 not only mediates host responses to infection and alloantigens but can also stimulate the secretion of ACTH from the anterior pituitary gland, acting directly on normal pituitary cells or by stimulating the release of a corticotropin-releasing factor from the hypothalamus. The production and secretion of glucocorticoid hormones themselves can regulate the intensity of immune reaction. It is likely that halothane affects these events; proof of this, however, is lacking. Of particular importance among the efferent pathways known to be affected by halothane anesthesia are those related to dopaminergic, serotonergic, and the autonomic nervous systems. These systems are immunomodulatory (28,29), with effects mediated through the hypothalamo-hypophyseal-adrenal axis (30) or by direct neural contact with lymphatic organs and cells (31). Our knowledge of the relationship of halothane anesthesia to the extensive network of other immunomodulatory substances (neurotransmitters, endorphins, enkephalins, etc. [32]) is, however, still scanty. Although the mechanism of its induction remains unknown, our data show that halothane anesthesia by itself leads to tl development of immunosuppression.

In clinical practice halothane anesthesia is usua followed by operative stress. In this study we inte tionally used as "stress" a laparotomy, an operati which mimics the clinical situation. Other forms experimentally induced stresses are known to aff immune functions (22,23,33). In our experimer laparotomy without prolonged halothane anesthe (group IIB) did not affect the growth of Sa I, and ev in the combination with halothane anesthesia (gro IA) surgical stress did not potentiate the immunosu pression produced by halothane alone. These resu differ from those found in the same experimen model when the humoral immune response w tested (6). There laparotomy potentiated the imm nosuppression provoked by halothane anesthes The failure of laparotomy by itself to affect the cellul type of immune response is probably related to t fact that a certain degree of tissue destruction needed to trigger suppressive mechanisms in t rejection of allogeneic tumor cells. Accordingly, m jor operations are usually followed by an increas postoperative depression of cell-mediated functio (4,34,35) and longer impairment of IL-2 production peripheral blood mononuclear cells (36). Although these situations the effects of prolonged anesthe cannot be ruled out, experimental models confi that greater surgical stress (like amputation of o hind limb) may alone be followed by the generati of suppressor cells (22) and impairment of NKC (23). Another possible explanation of the lack of a additional immunosuppressive effect of stress combination with halothane anesthesia in o present experiments is the fact that laparotomy w used as a stressor. This type of "stress" is followed reparatory processes that usually trigger mark changes in the immune homeostasis, owing to t mobilization of cells with morphogenetic functio (37). During wound healing and regenerati growth, the expression of class II antigens on mul ple cells occurs (38), enabling them to act as ne APC. Owing to the previously described possibil that host APC potentiate through the activation o helper cells the effects of cytolytic T cells on Sa (11–13), it is apparent that laparotomy may ev facilitate the process of tumor rejection. Our resul in group IIA, showing that laparotomy may minimi the immunosuppressive effect of halothane point such a possibility.

In conclusion, our evidence indicates that hal thane anesthesia alone induces immunosuppressio which may enhance the growth of allogeneic sarco in mice. Stress by laparotomy does not potenti immunosuppression, but may rather act as a factor that abrogates the immunosuppressive effect of halothane.

Although more evidence is needed in order to clarify the significance of halothane-induced suppression of the mechanisms involved in tumor rejection, it is clear that the findings obtained here have important clinical implications.

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References

1. Walton B. Effects of anaesthesia and surgery on immune status. Br J Anaesth 1979;51:37–43.
2. Graham CW. Immunological and carcinogenic side effects of anesthetics. Int Anesthesiol Clin 1980;18:173–86.
3. Gupta S. Immune response following surgical trauma. Crit Care Clin 1987;3:405–15.
4. Udović-Širola M, Radošević-Stašić B, Ribarić L, et al. The effect of general endotracheal and epidural anaesthesia on the immune status. Period Biol 1983;85:115–7.
5. Humphrey LJ, Wingard DW, Lang R. The effect of surgery and anesthesia on the immunologic responsiveness of the rat. Surgery 1969;65:946–51.
6. Radošević-Stašić B, Udović-Širola M, Polić L, et al. Humoral immunity of mice subjected to isolated or combined effects of halothane and operative stress. Period Biol 1986;88:24–6.
7. Cullen BF, Sundsmo JS. Failure of halothane anesthesia to alter growth of sarcoma in mice. Anesthesiology 1974;41:580–4.
8. Dallman MJ, Mason DW, Webb M. The role of host and donor cells in the rejection of skin allografts by T cell-deprived rats injected with syngeneic T cells. Eur J Immunol 1982;12:511–8.
9. Rock KL, Barnes MC, Germain RN, et al. The role of Ia molecules in the activation of T lymphocytes: II. Ia restricted recognition of allo K/D antigens is required for class I MHC stimulated mixed lymphocyte responses. J Immunol 1983; 130:457–62.
10. Mizouchi T, Golding H, Rosenberg AS, et al. Both $L_3T_4^+$ and Lyt-2^+ helper T cells initiate cytotoxic T lymphocyte responses against allogeneic major histocompatibility antigens but not against trinitrophenyl-modified self. J Exp Med 1985;162:427–43.
11. Singer A, Kruisbeek AM, Andrysiak PM. T cell-accessory cell interactions that initiate allospecific cytotoxic T lymphocyte responses: existence of both Ia-restricted and Ia-unrestricted cellular interaction pathways. J Immunol 1984;132:2199–209.
12. Goldin H, Singer A. Role of accessory cell processing and presentation of shed H-2 alloantigens in allospecific cytotoxic T lymphocyte responses. J Immunol 1984;133:597–605.
13. Smith DM, Stuart FP, Wemhoff GA, et al. Cellular pathways for rejection of class I-MHC-disparate skin and tumor allografts. Transplantation 1988;45:168–75.
14. Kinsky R, Duc H, Chaouat G, et al. Involvement of suppressor cells in active enhancement of allografted tumors. In vivo (adoptive transfer) and in vitro (MLR) evaluation. Synergy with enhancing antibodies. Cell Immunol 1981;58:107–23.
15. Bruce DL. Effect of halothane anesthesia on experimental Salmonella peritonitis in mice. J Surg Res 1967;7:180–5.
16. Saba TM. Mechanism mediating reticuloendothelial system depression after surgery. Proc Soc Exp Med Biol 1970;133: 1132–6.
17. Moudgil GC, Allan RB, Russel RJ, et al. Inhibition by anaesthetic agents of human leucocyte locomotion towards chemical attractants. Br J Anaesth 1977;49:97–105.
18. Cullen BF, Sample WF, Chretien PB. The effect of halothane on phytohemagglutinin-induced transformation of human lymphocytes in vitro. Anesthesiology 1972;36:206–12.
19. Cullen BF, Duncan PG, Ray-Keil L. Inhibition of cell-mediated cytotoxicity by halothane and nitrous oxide. Anesthesiology 1976;44:386–90.
20. Miyazaki S, Akiyoshi T, Arinaga S, et al. Depression of the generation of cell-mediated cytotoxicity by suppressor cells after surgery. Clin Exp Immunol 1983;54:573–9.
21. Vose BM, Moudgill GC. Postoperative depression of antibody-dependent cellular cytotoxicity following minor surgery and anesthesia. Immunology 1976;30:123–8.
22. Wang BS, Heacock EH, Wu AVO, et al. Generation of suppressor cells in mice after surgical trauma. J Clin Invest 1980;66:200–9.
23. Pollock RE, Lotzova E, Stanford SD, et al. Effect of surgical stress on murine natural killer cell cytotoxicity. J Immunol 1987;138:171–8.
24. Lewis RE, Cruse JM, Hazelwood J. Halothane-induced suppression of cell-mediated immunity in normal and tumor-bearing C_3H_f/H_e mice. Anesth Analg 1980;59:666–71.
25. Kusyk CJ, Hsu TC. Mitotic anomalies induced by three inhalation halogenated anesthetics. Environ Res 1976;11:366–70.
26. Blalock JE, Smith E. A complete regulatory loop between the immune and neuroendocrine system. Fed Proc 1985;44:108–11.
27. Lumpkin MD. The regulation of ACTH secretion by IL-1. Science 1987;238:452–4.
28. Hadden JW. Neuroendocrine modulation of the thymus-dependent immune systems. Ann NY Acad Sci 1986;496:39–48.
29. Paavonen T. Hormonal regulation of lymphocyte functions. Med Biol 1987;65:229–40.
30. Devoino L, Idova G, Alperina E, et al. Distribution of immunocompetent cells underlying psychoneuroimmunomodulation. Ann NY Acad Sci 1986;496:292–300.
31. Hall NR, Goldstein AL. Neurotransmitters and the immune system. In: Ader R, ed. Psychoneuroimmunology. New York: Academic Press, 1981:521–43.
32. Morley JE, Kay NE, Solomon GE, et al. Neuropeptides: conductors of the immune orchestra. Life Sci 1987;41:527–44.
33. Riley V. Psychoneuroendocrine influences on immunocompetence and neoplasia. Science 1981;212:1100–9.
34. Berenbaum MC, Fluck PA, Hurst NP. Depression of lymphocyte responses after surgical trauma. Br J Exp Pathol 1973; 54:597–607.
35. Keller SE, Weiss JM, Schleifer SJ, et al Suppression of immunity by stress: effect of a graded series of stressors on lymphocyte stimulation in the rat. Science 1981;213:1397–1400.
36. Akiyoshi T, Koba F, Arinaga S, et al. Impaired production of interleukin-2 after surgery. Clin Exp Immunol 1985;59:45–9.
37. Burch PRJ. Is normal growth regulated by a central system? In: MTP Press, ed. The biology of cancer—a new approach. Lancaster: St-Leonard's House, 1976:17–40.
38. Jonjić S, Radošević-Stašić B, Ćuk M, et al. Class II antigens induction in the regenerating liver of rats after partial hepatectomy. Transplantation 1987;44:165–8.

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Effect of Isoflurane on the Extent of Myocardial Necrosis and on Systemic Hemodynamics, Regional Myocardial Blood Flow, and Regional Myocardial Metabolism in Dogs after Coronary Artery Occlusion

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DAVIS RF, SIDI A. Effect of isoflurane on the extent of myocardial necrosis and on systemic hemodynamics, regional myocardial blood flow, and regional myocardial metabolism in dogs after coronary artery occlusion. Anesth Analg 1989;69:575–86.

Anesthetized dogs were studied in two protocols to determine the effect of isoflurane on the extent of myocardial injury resulting from left anterior descending coronary artery (LAD) occlusion. In 22 dogs (11 treated with isoflurane 1% inspired, beginning 1 hr after LAD occlusion, and 11 control) myocardial infarct size measured postmortem after 6 hr of LAD occlusion was significantly less with isoflurane than without it, 23.4 ± 3.8% vs 36.2 ± 2.4% of left ventricle; regional myocardial blood flow (RMBF) did not differ between groups and hemodynamic differences were slight. Fifty-two other dogs underwent two 15-min periods of LAD occlusion separated by 1 hr of reperfusion. Without isoflurane (n = 12), hemodynamic, RMBF, and regional metabolic data did not differ between the two occlusion periods. When isoflurane 1.3% inspired was administered during one of the two occlusion periods by random assignment, coronary perfusion pressure, left ventricular stroke work index, and systolic left ventricular pressure decreased more than when isoflurane was not administered. Both oxygen (O_2) consumption and supply in ischemic myocardium decreased proportionately during LAD occlusion, but more so with isoflurane. Neither lactate production, potassium release, glucose extraction, nor coronary venous carbon dioxide (CO_2) or O_2 content differed between LAD occlusion periods with and without isoflurane. Thus, isoflurane decreased the extent of myocardial necrosis produced by LAD occlusion but neither RMBF nor metabolic indications were improved during transitory ischemia.

Key Words: ANESTHETICS, VOLATILE—isoflurane. HEART, ISCHEMIA—isoflurane.

The interactions of ischemic heart disease, intraoperative myocardial ischemia, and postoperative cardiovascular morbidity mandate a precise understanding of the interactions between anesthetics and myocardial ischemia (1–6). Isoflurane decreases myocardial contractility; however, at equipotent doses, isoflurane appears to depress myocardial contractility less than either halothane or enflurane in intact animals (7). Systemic vascular resistance is decreased more by isoflurane than by either halothane or enflurane. Isoflurane decreases total body oxygen (O_2) consumption, and a major component of this decrease is in the myocardium (8). In normally perfused myocardium, regional myocardial blood flow (RMBF) changes in proportion to local O_2 consumption (9), but with isoflurane coronary vascular resistance is decreased and RMBF maintained in spite of the decreased myocardial O_2 consumption (10). Such coronary vasodilation can adversely redistribute RMBF, impair regional oxygenation, and produce both anaerobic metabolism with net lactate production and depressed contractile function in myocardial areas distal to arterial obstruction (11–14).

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Previous laboratory investigations have demonstrated that pharmacologic and physiologic interventions can decrease the extent of myocardial infarction during acute coronary artery occlusion (15). Both general anesthesia with halothane and regional anesthesia with thoracic epidural lidocaine decrease ST segment elevation and decrease myocardial infarct size in dogs (16–18). The present study was designed to test whether clinically useful concentrations of isoflurane have a myocardial salvage effect similar to that of halothane or a deleterious effect due to an adverse redistribution of coronary blood flow in a canine model of acute evolving myocardial infarction produced by coronary artery occlusion. The data are from two protocols that have examined the effect of isoflurane on myocardial infarct size, on systemic hemodynamic performance, on RMBF, and on regional myocardial metabolism, acid–base status, and electrolyte balance in dogs with myocardial ischemia produced by left anterior descending coronary artery (LAD) occlusion.

Materials and Methods

Adult mongrel dogs of either sex (weighing 19.3 ± 2.4, [SD] kg) were anesthetized with intravenous thiamylal, 15 mg/kg, followed by a continuous thiamylal infusion of 1 to 4 $mg \cdot kg^{-1} \cdot hr^{-1}$. Mechanical ventilation with an air/O_2 mixture was adjusted to maintain normoxia and normocarbia. The pulmonary artery (PA) and aorta (Ao) were catheterized from the femoral vein and artery, respectively. Cardiac output (CO) was measured by the thermodilution technique using 5 mL of iced (<4°C) injectate and a computer (Model 9520A, Edwards Laboratories, Santa Ana, CA); the value recorded was the mean of three consecutive determinations made within 3 min, and each injection occurred during a brief period of apnea.

After a left fifth interspace thoracotomy, the heart was suspended in a pericardial cradle. The left ventricle was cannulated from the left atrium (LA) with a transducer-tipped catheter to measure pressure in the left ventricle (LV) and its first time derivative (LV dP/dt). An additional catheter was inserted into the LA for microsphere injection. The left anterior descending coronary artery (LAD) was isolated proximal to the first major apical, diagonal branch and loosely encircled with a silastic ligature. Before LAD occlusion with the ligature, all dogs received lidocaine, 1 mg/kg. The dogs were arbitrarily assigned to one of two experimental protocols, one to measure myocardial infarct size and one to examine in detail the effects of a short interval of myocardial ischemia.

Electrocardiogram (ECG, standard lead II), heart rate, LV dP/dt, and aortic (Ao), pulmonary arterial (PA), and LV pressures (systolic, diastolic, and mean) were recorded with calibrated transducers (Model P50, Gould Statham, Inc., Oxnard, CA) in conjunction with a polygraph. Transducers and the corresponding intravascular sites were connected with 1.2 m of saline-filled polyethylene tubing (Cobe Laboratories, Inc., Lakewood, CO), except for LV pressure, which was measured with a transducer-tipped catheter (Model MPC-500, Millar Instruments, Inc., Houston, TX). Transducers were calibrated with a mercury manometer and checked for zero position drift before each measurement; the directly visualized LA was taken as the zero reference for transducer calibration. End-diastolic pressure in the LV (LVEDP) was taken as the LV pressure immediately before the "A" wave, LV dP/dt was obtained by electronic differentiation of LV pressure, and maximal positive deflection of the LV dP/dt waveform was recorded for each measurement interval.

Calculated variables included cardiac index (CI), stroke index (SI), coronary perfusion pressure (CPP) (calculated as Ao diastolic − LVEDP), left ventricular stroke work index (LVSWI), tension time index (TTI, calculated from planimetric measurement of the area under the LV pressure waveform from the beginning of the rapid upstroke to the dicrotic notch of the Ao pressure wave), and systemic (SVR) and pulmonary (PVR) vascular resistances. Coronary vascular resistance (CVR) was calculated from CPP and RMBF. All calculations were made using standard formulas (19).

In both groups, RMBF was measured by using approximately 1.5 × 10^6 15-μm-diameter microspheres (MS); four isotopes were selected from ^{95}Nb, ^{85}Sr, ^{46}Sc, ^{51}Cr, and ^{141}Ce in a randomized sequence. The MS were injected into the LA over 20 sec, immediately after which the injecting syringe and tubing were flushed with 10 mL of normal saline. This number of MS was used to provide approximately 600 MS/g of myocardium, assuming a CO of 2.5 L/min and normal RMBF, approximately 1 $mL \cdot g^{-1} \cdot min^{-1}$. A reference sample of arterial blood was aspirated from the Ao at a constant rate (22.9 mL/min) by a Harvard pump, beginning 15 sec before microsphere injection and continuing for 2 min. At the end of the experiment, transmural samples of LV myocardium (approximately 3–4 g each) were obtained from normal-appearing myocardium outside the distribution of the occluded vessel and from cyanotic myocardium within the distribution of the occluded vessel. Infarct staining guided the myocardial sampling in the infarct size protocol. Three samples of myocardial tissue were taken from each area; each sample was divided into endocardial and epicardial halves, which were weighed individually. The reference blood samples and the myocardial tissue samples were placed into polyethylene tubes and the radioactive emissions were measured with an LKB Wallach gamma counter (Model 1282, Compugamma, Turku, Finland). Correction of emission data for background and Compton crossover was done on line by the gamma counter. RMBF was calculated from the emission data by accepted techniques (20). For each heart, a single value for transmural, endocardial and epicardial (endo and epi, respectively) RMBF was calculated for ischemic and normal myocardial regions by weighted averaging of the emission data from each tissue sample; the endo/epi RMBF ratio was calculated for each region of the myocardium for each dog. The transmural RMBF values reported, therefore, represent an approximately 6-g sample of myocardium, and RMBF values approximately 20% of normal would be derived from a tissue sample containing 350 to 400 MS.

Infarct Size Protocol

All dogs in this protocol underwent complete LAD occlusion at the previously selected location. RMBF was measured before LAD occlusion, 1 hr after LAD occlusion before treatment, and during treatment 3 and 6 hr after occlusion. CO was measured and blood was sampled from the Ao for arterial blood gas analysis every hour beginning with the first RMBF measurement. Five minutes after LAD occlusion, 600,000 macroaggregated albumin MS (3-M Co., Eagan, MN) labeled with technetium 99m (0.5 mCi/kg) were injected into the LA to delineate the distribution of coronary blood flow at that point in time by subsequently performed autoradiography (21). One hour after LAD occlusion, dogs were assigned randomly to continue receiving either thiamylal infusion alone (control group) or combined thiamylal infusion and isoflurane, 1% inspired, delivered by a previously calibrated vaporizer (treatment group).

Six hours after LAD occlusion, the dogs were given a lethal intravenous dose of thiamylal followed by a sufficient volume of a standard solution of KCl to produce cardiac arrest. After removing the heart, the distance from the LAD aortic ostium to the site of occlusion and the presence of total LAD occlusion were measured and confirmed, respectively, by insertion of a probe (0.035-in. intravascular guide wire). The LV, including the interventricular septum, was dissected free of right ventricular, atrial, and valvular tissues. The hearts were then sectioned into 0.5-cm-thick slices parallel to the atrioventricular groove to obtain six to eight sections of LV myocardium distal and one to two sections proximal to the ligature. The sections were then incubated in a fresh 1% solution of triphenyl tetrazolium chloride (TTC) for 30 min at 37°C to delineate the infarct area (22). The TTC stain was enhanced after the 30-min incubation by immersing the tissue in a 10% formalin saline solution. After TTC staining, the tissue slices were placed into standard radiographic cassettes to produce the autoradiographic image of the distribution of the technetium-labeled albumin MS that had been injected after LAD occlusion. A specimen of right ventricular free wall was weighed and then treated with the TTC and formalin and placed into the x-ray cassettes with the LV sections. This right ventricular specimen was reweighed after removal from the x-ray cassettes. The ratio of fresh weight to the subsequent weight was used to correct the LV tissue weights used in the RMBF calculations.

After exposure of the film, the tissue sections were removed from the cassette and the film was developed. Tracings from the basal and apical surface of each tissue section were drawn on transparent sheets to indicate the boundary between normal (TTC positive) and infarcted (TTC negative) myocardium; similar transparent tracings were made for the autoradiographic image of each tissue section. An electronic digitizer was used to determine the percentage of the surface area of each tissue section occupied by infarction using the tracings. The tracings of the autoradiograms were similarly digitized to measure the area of each section not containing technetium 99m, which was taken as the hypoperfused area produced by LAD occlusion and, therefore, the area at risk for infarction. Using these data, infarct size was expressed both as a percentage of the total LV area and as a percentage of the risk area. The tissue sections were then dissected to physically separate normal and infarcted myocardium to enable direct measurement of infarct size as the weight of the infarcted tissue, also expressed as a percentage of the total LV weight. Thus, infarct size was measured by three methods representing two independent techniques. Finally, samples of myocardium were taken from myocardial regions stained by TTC (normal) and from regions unstained by TTC (infarct) for RMBF measurements as described above.

Intermittent Ischemia Protocol

Reversible acute ischemia was produced by totally occluding the LAD using the silastic ligature for 15 min. Each experiment consisted of two observation periods during which data were obtained before LAD occlusion and after 15 min of LAD occlusion but before reopening the LAD for reperfusion. One hour of reperfusion was allowed between the two observation periods. Isoflurane (1.3% inspired), beginning after the preocclusion measurements and sampling, was administered during one of the two observation periods, by random assignment. In a subgroup of animals isoflurane was not administered during either observation period in order to evaluate the time-related effects in this sequential occlusion model.

At the time intervals noted above, hemodynamics were measured and blood was sampled from Ao, PA, LAD distal to the tourniquet, LAD companion vein at the same level (LADv), and distal circumflex vein (CXv). A coronary artery and vein were cannulated for this sampling using a modified Seldinger technique with a 0.015-in.-diameter guidewire. This technique and its effect on RMBF are described elsewhere (23). Pressure in the distal LAD was measured by means of the LAD catheter connected to the transducer system described earlier. The difference between calculated CPP and distal LAD diastolic pressure during LAD occlusion was calculated; this calculated value was assumed to represent the coronary collateral perfusion pressure (CCP). Blood samples were analyzed for gas tensions (Po_2 and Pco_2), pH, and concentrations of glucose, lactate, sodium, and potassium. Base excess (BE) or deficit was calculated from pH and Pco_2. Blood gas tensions and pH were measured with a calibrated laboratory analyzer (Model 713, Instrumentation Laboratory, Inc., Lexington, MA). Arterial (Sao_2) and venous (Svo_2) oxygen saturation and content (Cao_2 and Cvo_2, respectively) were measured with a cooximeter (Model IL-282, Instrumentation Laboratory Inc., Lexington, MA). Lactate concentrations were measured using a specific membrane-bound-enzyme electrode (Yellow Springs Instrument Co., Inc., Model 27). Glucose was measured (Accu-check bG Model 790, Bio Dynamics, Inc., Indianapolis, IN) and electrolytes (K, Na) were determined by flame photometry (Model 143, Instrumentation Laboratory, Inc., Lexington, MA). Because of difficulties with equipment availability and in obtaining a sufficient volume of coronary blood during ischemia, all analyses could not be performed during all experiments.

The epicardial electrogram was obtained from 15 locations on the anterior surface of the LV; sites were selected for ECG mapping so that each was located near an epicardial landmark, such as an arterial bifurcation, to ensure reproducible placement of the electrode. The epicardial ECG was obtained with a unipolar, hand-held electrode connected to an ECG amplifier calibrated to a sensitivity of 1 mV/mm; a recorder speed of 25 mm/sec was used (24). Regions adjacent to epicardial dissection or catheter placement were not used to prevent ECG artifacts caused by trauma to the epicardium. The ST-segment elevation was measured 0.04 sec after the end of the QRS complex. Epicardial sites were not used when the QRS was longer than 0.065 sec because epicardial ST-segment elevation as an index of ischemia is invalidated by intraventricular conduction abnormalities (25). The ECG data are expressed both as the sum of ST-segment elevations from each site in millivolts ($\Sigma - \mathrm{ST}$) and as the number of epicardial sites with ST elevation greater than 1 mV ($n - \mathrm{ST}$).

Statistical Methods

In both protocols, data from each animal were collated to allow grouped comparison of control and treatment groups. The null hypothesis that isoflurane had no influence was tested in both protocols. Infarct size data (not time-dependent) were compared between control and treatment groups using Student's *t*-test for grouped data. Time-dependent data (repeated measurements) were compared within and between groups by repeated measures analysis of variance (ANOVA PC, Human Systems Dynamics, Northridge, CA). When the analysis of variance indicated significant variability due to time or treatment, sequential *t*-tests using the Bonferroni correction were applied to specific comparisons. Results are expressed as mean values ± 1 SEM. A probability of chance occurrence less than 5% ($P < 0.05$) was considered significant. For the infarct size protocol, least squares linear regression techniques were used to compare data for infarct size measurements by weight of tissue (% of LV) and planimetered area (% of LV). All relevant institutional policies regarding the care of laboratory animals were followed in these experiments.

Results

Infarct Size Protocol

A total of 26 dogs was assigned to this protocol; four died due to ventricular fibrillation (three control dogs and one treatment dog) during the study and were excluded from analysis. These mortality rates were not significantly different between the two groups. Myocardial infarct size (all three measurements) was significantly smaller in dogs treated with isoflurane

Table 1. Effect of Isoflurane on Myocardial Infarct Size

	Control ($n = 11$)	Isoflurane ($n = 11$)
Body weight (kg)	19.7 ± 0.8	22.2 ± 0.8
Risk area (% of left ventricle)	32.2 ± 2.8	26.4 ± 2.1
Infarct size		
% of left ventricular area	31.1 ± 2.0	21.0 ± 3.2*
% of left ventricular weight	36.2 ± 2.4	23.4 ± 3.8*
% of risk area	101.9 ± 8.6	77.0 ± 7.9*

Values are mean ± SEM.
*$P < 0.05$ when compared with the control.

than in control dogs. No significant difference in body weight was seen in the two groups (Table 1). The relationship between infarct size measured by planimetry and that measured by tissue weight is given by the regression equation: area = 1.02 (weight) + 2.63, R = 0.903.

Stroke volume and CI were greater and SVR less at 3 and 6 hr after LAD occlusion with isoflurane than without it (Table 2). Both LV dP/dt and LVSWI decreased over the 6 hr but did not differ between the groups (Table 2). Likewise, significant intergroup differences for HR or CPP did not occur, although CPP was lower after the 6-hr measurement than before LAD occlusion in the isoflurane group, but not in the control group. Arterial blood gas tensions were not affected in either group at any time (Table 2). RMBF decreased in the ischemic zone following LAD occlusion, but the ischemic RMBF values were not significantly different between the groups (Table 3). No statistically significant changes were seen in normal zone coronary vascular resistance. Ischemic zone coronary vascular resistance was numerically increased in both groups following LAD occlusion.

Intermittent Ischemia Protocol

Among the 12 dogs that received no isoflurane during either observation period, regional myocardial metabolism was assessed in seven and RMBF measurements were made in five. Isoflurane was administered to 40 dogs during one of the two observation periods. Systemic hemodynamics, ST segment mapping, RMBF, coronary blood gas tension, and pH measurements were performed in 19 of these dogs; lactate and glucose in coronary blood were measured in 11 of these dogs; and sodium and potassium in coronary blood were measured in 10 of these dogs.

The hemodynamic and metabolic data obtained before ischemia (control) did not differ between the two observation periods for any of the subgroups described above. During ischemia, however, systolic left ventricular pressure (SLVP), CPP, LV dP/dt, LVSWI, and SVR decreased below baseline values more with isoflurane than without it (Table 4). Data from the epicardial ECG mapping showed that both $n - \text{ST}$ and $\Sigma - \text{ST}$ increased with LAD occlusion but the magnitude of these changes was unaffected by isoflurane; preocclusion values were not different comparing observation period 1 to observation period 2. Heart rate and LVEDP were not affected by ischemia or isoflurane. During LAD occlusion with isoflurane SVR was less than at the corresponding time without isoflurane (Table 4), but isoflurane did not significantly affect CVR values in the circumflex perfusion area (Table 5). Neither mean LAD pressure distal to the occlusion nor CVR in the LAD perfusion zone was affected by isoflurane during LAD occlusion (Figure 1, Table 5). The CCP during LAD occlusion was lower with isoflurane than without it (Table 4), but calculated collateral resistance (CCP/RMBF × 79.8) was 682 ± 170 dynes$\cdot$sec$^{-1}\cdot$cm^{-5} without isoflurane and 429 ± 87 with isoflurane—not a significant difference.

Lactate extraction by the myocardium became negative (indicating net production) in the LAD perfusion bed during LAD occlusion and the magnitude of this change was unaffected by isoflurane (Figure 2). Lactate extraction decreased but remained positive in the nonischemic perfusion bed (Ao − CXv) during both ischemic periods but was not different with or without isoflurane (Figure 2). Glucose extraction in the LAD region increased during LAD occlusion in both groups, but was not changed in the circumflex region during either LAD occlusion period (Figure 3). The RMBF values for this protocol are shown in Table 5. Oxygen supply ($\text{Ca}o_2$ × RMBF) in the circumflex region was unaffected by LAD occlusion. In the LAD zone, both O_2 supply and O_2 consumption decreased during LAD occlusion (Table 6). These decreases were greater with isoflurane than without it, but O_2 utilization (the ratio of O_2 supply to O_2 consumption) in the LAD perfusion zone was not affected by isoflurane during LAD occlusion (Table 6). The acid base and electrolyte data from this protocol are shown in Table 7.

Among the seven dogs in which coronary catheters were inserted and which received no isoflurane, hemodynamic, metabolic, acid–base, and electrolyte parameters did not differ significantly before or during LAD occlusion between the first and second observation periods. Likewise, among the five dogs in which RMBF values were measured but isoflurane was not administered, RMBF values did not differ between observation periods.

Table 2. Effects of Isoflurane on Hemodynamic Variables and Arterial Blood Gas Tensions before and during a 6-hr Period of Complete Left Anterior Descending Coronary Artery Occlusion

	Time after left anterior descending coronary artery occlusion (hr)							
	Control ($n = 11$)				Isoflurane ($n = 11$)			
	0	1	3	6	0	1	3	6
CPP (mm Hg)	99 ± 5	80 ± 6	97 ± 3	82 ± 6	93 ± 5	91 ± 5	81 ± 5	69 ± 4*
AO (mm Hg)	150 ± 4	140 ± 7	140 ± 4	128 ± 7*	153 ± 11	147 ± 7	126 ± 7	116 ± 6*
LVEDP (mm Hg)	5.2 ± 1.1	7.9 ± 1.7	7.2 ± 1.4	6.6 ± 1.5	5.5 ± 1.1	6.3 ± 1.1	7.6 ± 1.4	6.8 ± 1.6
HR (beats/min)	138 ± 9	142 ± 9	148 ± 6	155 ± 9	136 ± 8	131 ± 6	138 ± 5	147 ± 5
SV (mL)	20.7 ± 2.0	17.3 ± 2.2	10.5 ± 0.8*	8.7 ± 1.2*	18.9 ± 1.9	20.5 ± 2.5	16.9 ± 1.3†	13.2 ± 2.2*†
CI ($\mathrm{mL{\cdot}min^{-1}{\cdot}m^{-2}}$)	3470 ± 163	3027 ± 344	2001 ± 172*	1662 ± 197*	3146 ± 338	3053 ± 335	2691 ± 237†	2133 ± 244*†
SVR ($\mathrm{dynes{\cdot}sec{\cdot}cm^{-5}}$)	3652 ± 239	3928 ± 361	6354 ± 438*	7016 ± 639*	3813 ± 359	3933 ± 415	3826 ± 395†	4485 ± 506†
LV dP/dt (mm Hg/sec)	2269 ± 306	1850 ± 196	1750 ± 265*	1521 ± 178*	2990 ± 606	2253 ± 275	1847 ± 158*	1943 ± 249*
LVSWI ($\mathrm{g{\cdot}m^{-1}{\cdot}min^{-1}}$)	54.5 ± 4.5	43.7 ± 6.9	26.3 ± 2.5*	20.7 ± 3.7*	47.0 ± 7.2	47.2 ± 5.0	33.2 ± 2.8*	24.3 ± 3.8*
$\mathrm{Pao_2}$ (mm Hg)	115 ± 18	118 ± 24	122 ± 9	101 ± 6	146 ± 22	105 ± 10	114 ± 9	114 ± 9
$\mathrm{Paco_2}$ (mm Hg)	37 ± 3	40 ± 3	32 ± 2	34 ± 2	36 ± 3	38 ± 2	38 ± 2	35 ± 1
pH (units)	7.38 ± 0.02	7.34 ± 0.02	7.40 ± 0.02	7.34 ± 0.02	7.36 ± 0.03	7.33 ± 0.03	7.36 ± 0.02	7.33 ± 0.02

Values are mean ± SEM. Abbreviations: CPP, coronary perfusion pressure; AO, aortic systolic pressure; LVEDP, end-diastolic pressure in the left ventricle; HR, heart rate; SV, stroke volume; CI, cardiac index; SVR, systemic vascular resistance; LV dP/dt, maximum positive left ventricular dP/dt; LVSWI, left ventricular stroke work index.

*$P < 0.05$ when compared with time zero in the same group.

†$P < 0.05$ when compared with the same time in the control group.

Table 3. Effect of Left Anterior Descending Artery Occlusion on Regional Myocardial Blood Flow (RMBF), Transmural Blood Flow Distribution, and Coronary Vascular Resistance with and without Isoflurane

	Time after left anterior descending coronary artery occlusion (hr)							
	Control ($n = 11$)				Isoflurane ($n = 11$)			
	0	1	3	6	0	1	3	6
RMBF ($\mathrm{ml{\cdot}min^{-1}{\cdot}100\ g^{-1}}$)								
Normal zone	120 ± 23	133 ± 25	99 ± 26	102 ± 22	126 ± 13	94 ± 5	96 ± 9	88 ± 12
Infarct zone	124 ± 27	28 ± 14*†	27 ± 14*†	26 ± 15*†	128 ± 15	34 ± 7*†	34 ± 9*†	24 ± 6*†
Endo:epi ratio								
Normal zone	1.19 ± 0.08	1.14 ± 0.04	1.23 ± 0.06	1.06 ± 0.09	1.20 ± 0.05	1.15 ± 0.07	1.13 ± 0.07	1.03 ± 0.07
Infarct zone	1.08 ± 0.15	0.55 ± 0.11*†	0.77 ± 0.14*†	0.63 ± 0.15*†	0.98 ± 0.04	0.59 ± 0.11*†	0.63 ± 0.11*†	0.69 ± 0.11*†
Coronary vascular resistance ($\mathrm{dynes{\cdot}sec^{-1}{\cdot}cm^{-5}}$)								
Normal zone	82 ± 18	56 ± 12	89 ± 14	79 ± 16	63 ± 7	79 ± 7	68 ± 6	68 ± 8
Infarct zone	80 ± 18	517 ± 191	632 ± 206	1209 ± 583	61 ± 6	276 ± 55*†	273 ± 66*†	302 ± 58*†

Values are mean ± SEM.

*$P < 0.05$ compared with corresponding time zero value.

†$P < 0.05$ compared with corresponding normal zone value.

Discussion

Infarct Protocol

The principal finding of this portion of our study is that myocardial infarct size was significantly smaller in the isoflurane-treated animals than in control animals. The myocardial salvage was evident even when data were normalized for the size of the ischemic zone (Table 1) and despite the 1-hr interval between LAD occlusion and the initiation of isoflurane treatment. Although no direct measurements of myocardial O_2 consumption were made in this protocol, there were no differences between the control group and the isoflurane group in hemodynamic correlates of myocardial O_2 consumption. The relative preservation of stroke volume (and, hence, CI) with isoflurane may be related to the fact that SVR did not increase markedly as it did in the control group. Despite better maintenance of systemic perfusion with isoflurane than without it, RMBF and O_2 supply to the ischemic area did not differ between groups. As our microsphere technique required the use of a

Table 4. Systemic Hemodynamic and Electrocardiographic Effects of Left Anterior Descending Coronary Artery Occlusion with and without Isoflurane

	Without isoflurane (n = 19)		With isoflurane (n = 19)	
	Before LAD occlusion	During LAD occlusion	Before LAD occlusion	During LAD occlusion
CPP (mm Hg)	91 ± 4.6	78 ± 6.2*	85 ± 5.0	56 ± 5.4*†
SLVP (mm Hg)	119 ± 4.7	105 ± 6.8*	115 ± 5.9	85 ± 5.8*†
LVEDP (mm Hg)	6.1 ± 0.7	7.9 ± 1.0	6.2 ± 1.0	8.3 ± 1.2
CoPP (mm Hg)		62 ± 4.9		46 ± 4.6†
LV dP/dt (mm Hg/sec)	3000 ± 340	2117 ± 257*	2957 ± 377	1509 ± 127*
LVSWI ($g \cdot m^{-1} \cdot beat^{-1}$)	31.6 ± 3.2	21.6 ± 2.7*	27.9 ± 2.7	15.0 ± 1.8*†
SI ($ml \cdot beat^{-1} \cdot m^{-2}$)	19.4 ± 1.6	15.0 ± 1.5*	17.8 ± 1.6	13.6 ± 1.4*
SVR ($mm\ Hg \cdot L^{-1} \cdot min^{-1}$)	4712 ± 410	5396 ± 427*	4878 ± 498	4451 ± 334†
HR (beats/min)	136 ± 4.4	135 ± 3.7	140 ± 3.6	137 ± 4.6
LVTTI ($mm\ Hg \cdot sec \cdot mm^{-1}$)	2467 ± 132	2305 ± 172	2562 ± 174	1993 ± 152*
Σ – ST (mV)	4.1 ± 1.4	21.7 ± 3.7*	3.5 ± 1.8	22.1 ± 4.1*
n – ST (sites)	1.2 ± 0.3	3.9 ± 0.5*	0.8 ± 0.3	3.7 ± 0.5*

Values are mean ± SEM. Abbreviations: LAD, left anterior descending coronary artery; CPP, coronary perfusion pressure; SLVP, systolic left ventricula pressure; LVEDP, left ventricular end-diastolic pressure; CoPP, collateral perfusion pressure; LV dP/dt, peak first time derivative of left ventricular pressur LVSWI, left ventricular stroke work index; SI, stroke index; SVR, systemic vascular resistance; HR, heart rate; LVTTI, left ventricular tension time index; n - ST, number of ST mapping sites with ST elevation ≥1 mV; and Σ – ST, total amount of ST elevation from all sites.

*$P < 0.05$ compared with before LAD occlusion value in the same group.

†$P < 0.05$ compared with corresponding value without isoflurane.

Table 5. Effects of Left Anterior Descending Coronary Artery Occlusion on Regional Myocardial Blood Flow with and without Isoflurane

	Without isoflurane (n = 19)		With isoflurane (n = 19)	
	Before LAD occlusion	During LAD occlusion	Before LAD occlusion	During LAD occlusion
		Circumflex Perfusion Zone		
RMBF ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	93 ± 8.6	85 ± 6.7	97 ± 9.9	88 ± 9.5
Endo:epi	1.15 ± 0.04	1.06 ± 0.06*	1.13 ± 0.04	0.98 ± 0.04
CVR mm Hg ($dynes \cdot sec^{-1} \cdot cm^{-5}$)	85 ± 6	78 ± 7	83 ± 10	60 ± 7
		LAD Perfusion Zone		
RMBF ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	76 ± 9.3	22 ± 5.7*	81 ± 8.4	15 ± 3.7*
Endo:epi	0.91 ± 0.05	0.68 ± 0.08*	0.93 ± 0.03	0.80 ± 0.06
CVR mm Hg ($dynes \cdot sec^{-1} \cdot cm^{-5}$)	124 ± 19	1172 ± 292*	101 ± 12	827 ± 180*

Values are mean ± SEM. Abbreviations: LAD, left anterior descending coronary artery; RMBF, regional myocardial blood flow; Endo:epi, endocardia epicardial RMBF ratio; and CVR, coronary vascular resistance.

*$P < 0.05$ compared with before LAD occlusion value in the same group.

†$P < 0.05$ compared with during LAD occlusion without isoflurane.

relatively large tissue sample, a change in RMBF that occurred in a narrow area at the edge of the infarct zone would not have been detected. In a similar previous investigation the primary area of myocardial salvage was seen at the lateral epicardial margins of the infarction (17). Thus, the apparent reduction of myocardial infarct size is not accounted for by a measured improvement in overall ischemic zone O_2 supply.

This protocol was intended to determine in an experimental model with a predictable outcome (infarct size) whether isoflurane produced a myocardial salvage similar to halothane or whether it produced any observable deleterious effect. The goal of this protocol was not necessarily to investigate a potentia therapeutic intervention for acute myocardial infarction, although one group has reported promisin initial results when general anesthesia was administered to patients undergoing nonsurgical myocardia reperfusion in the setting of acute myocardial infarction (26). The potential for a deleterious effect fron isoflurane in this model is an important consideratio given recent concerns about the use of isoflurane i patients with ischemic heart disease (27). There ar differences between the normal collateral patter comparing the human to the canine coronary system However, chronic coronary artery disease in human causes functional enhancement of collateral vessel

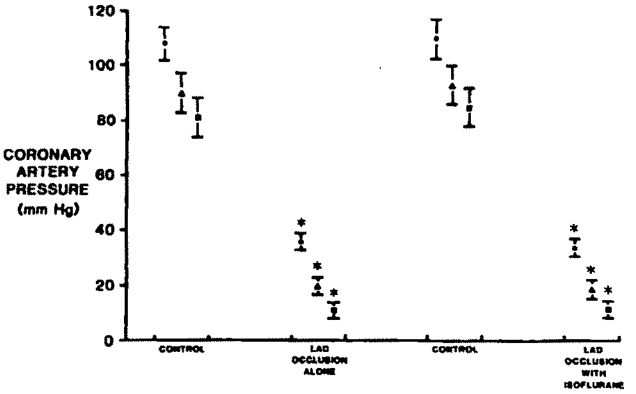

Figure 1. Coronary artery pressure (systolic [circle], diastolic [square], and mean [triangle]) measured distal to the left anterior descending artery occlusion site before (control) and during LAD occlusion with and without isoflurane. Values are means ± 1 SEM. Asterisk indicates $P < 0.05$ compared with corresponding value before LAD occlusion.

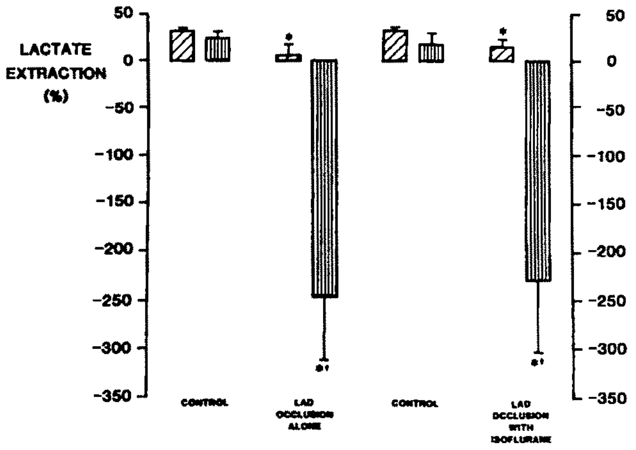

Figure 2. Lactate extraction (arteriovenous lactate concentration difference divided by arterial concentration expressed as a percent) for both the normally perfused myocardium (circumflex area [diagonal hatching]) and the ischemic myocardium (left anterior descending area, [vertical hatching]) before (control) and during left anterior descending artery occlusion alone and occlusion with isoflurane. Values shown are means ± 1 SEM. Asterisk indicates $P < 0.05$ when compared with the corresponding control value and the dagger $P < 0.05$ compared with the corresponding circumflex area value.

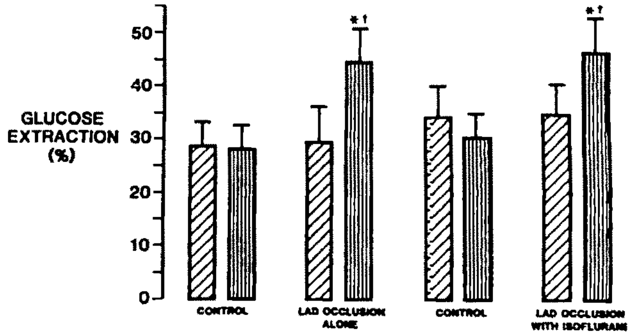

Figure 3. Glucose extraction (arteriovenous concentration difference divided by the arterial difference expressed as a percent) is shown before (control) and during left anterior descending artery occlusion with and without isoflurane for both the normally perfused myocardium (circumflex area [diagonal hatching]) and the ischemic myocardium (left anterior descending artery area [vertical hatching]). Values are means ± 1 SEM. Asterisk indicates $P < 0.05$ when compared with the corresponding control value, and the dagger indicates $P < 0.05$ compared with the corresponding circumflex area value.

(including epicardial), so that the normal canine situation mimics the human state with chronic coronary disease. Our data, obtained from the LV of dogs without prior collateral enhancement and with isolated total LAD occlusion, provide experimental evidence that isoflurane, under conditions of acute evolving myocardial infarction, will not necessarily have a deleterious effect and may, indeed, promote myocardial salvage.

The pathophysiologic progression of acute myocardial infarction begins with a regional reduction in nutritive blood flow relative to tissue needs. The progression to regional tissue hypoxia, anaerobic metabolism, reduction of high-energy phosphate stores, lactic acid production, and loss of muscle contraction is rapid. Evolution from cellular dysfunction to irreversible cellular damage and infarction is a slower process requiring several minutes to several hours, depending on detection techniques (i.e., ultrastructure or conventional histology) and the model. When assessed by loss of oxidative enzymes from the myocardium, the infarction process becomes uniform by 6 to 9 hr, but further quantitative enzyme release can continue for 48 hr (28). The method used to measure infarct size has been frequently applied, and, although it may not precisely account for irreversibly injured cells in the normally stained border zone, it appears to be reasonably accurate by 6 hr (29,30). Therefore, the 6-hr duration of this study is relatively brief; the resultant infarctions may have become larger if the animals had been observed for a longer time. Nevertheless, the decreased size of the infarct in dogs treated with isoflurane indicates that either the eventual extent of the infarction was limited or the time-course of the infarction process was delayed. This is an important distinction that cannot be made from the data we present. However, the goal of this protocol was to study an experimental model of the clinical situation, where anesthesia is necessary to perform a therapeutic or diagnostic procedure for a patient with acute myocardial ischemia at risk of developing a myocardial infarction. Importantly, in this context, either an interruption of the infarction process or a delay of its progression until reperfusion is accomplished could be beneficial. We conclude from this portion of our study that adding isoflurane to a thiamylal infusion significantly reduced myocardial infarct size and helped to preserve ventricular

Table 6. Oxygen Supply and Consumption in Area Perfused by the Left Anterior Descending Coronary Artery before and during Occlusion of the Artery with and without Isoflurane

	Without isoflurane (n = 19)		With isoflurane (n = 19)	
	Before LAD occlusion	During LAD occlusion	Before LAD occlusion	During LAD occlusion
Po$_2$ (mm Hg)				
LAD	132.7 ± 12.7	111.9 ± 13.6	122.2 ± 16.9	95.6 ± 12.3
LADv	25.6 ± 1.3	24.5 ± 2.2	24.6 ± 1.5	24.4 ± 1.9
Oxygen content (mL O$_2$/100 mL)				
LAD	16.0 ± 0.9	15.9 ± 1.1	15.8 ± 1.0	15.6 ± 1.0
LADv	6.2 ± 0.5	4.1 ± 0.6	5.2 ± 0.4	4.7 ± 0.5
Oxygen supply (mL·min^{-1}·100 g^{-1})	37.7 ± 4.4	10.3 ± 3.1*	41.8 ± 7.8	5.3 ± 1.1*†
Oxygen consumption (mL·min^{-1}·100 g^{-1})	29.2 ± 3.0	8.7 ± 2.7*	27.2 ± 3.6	3.5 ± 0.9*†
Oxygen utilization (%)	74 ± 3	74 ± 5	77 ± 4	72 ± 4

Values are mean ± SEM. Abbreviations: LAD, left anterior descending coronary artery; LADv, left anterior descending coronary artery companion vein at the same level.

*$P < 0.05$ compared with before LAD occlusion value of the same group.

†$P < 0.05$ compared with during LAD occlusion without isoflurane.

Table 7. Effects of Left Anterior Descending Coronary Artery Occlusion on Acid–Base and Electrolyte Blood Samples From the Left Anterior Descending Companion Vein

	Without isoflurane		With isoflurane	
	Before LAD occlusion	During LAD occlusion	Before LAD occlusion	During LAD occlusion
Pco$_2$ (mm Hg)				
LADv	52.3 ± 2.0	63.8 ± 3.7*	55.4 ± 3.2	67.7 ± 2.9
pH				
LADv	7.33 ± 0.02	7.19 ± 0.03*	7.32 ± 0.02	7.17 ± 0.02*
Electrolytes				
K (mEq/L)	2.74 ± 0.20	4.08 ± 0.33*	2.70 ± 0.20	4.06 ± 0.36*
K/Na (× 10^{-3})	17.6 ± 1.5	24.6 ± 2.2*	17.0 ± 1.5	24.8 ± 2.3*

Values are mean ± SEM. For Pco$_2$ and pH values, n = 19; for electrolyte values, n = 10. Abbreviations: LADv, left anterior descending coronary artery companion vein at the same level.

*$P < 0.05$ compared with before left anterior descending coronary artery occlusion value in the same group.

pump function in dogs after LAD occlusion, and that there was no deleterious effect of isoflurane in terms of animal mortality or RMBF.

Intermittent Ischemia Protocol

This protocol was designed to complement the infarct size protocol by providing details of effects that occur in the first 15 min of LAD occlusion in this animal model. The major finding of this protocol is the relative similarity of the important hemodynamic, RMBF, metabolic, and electrocardiographic effects of ischemia during LAD occlusion with and without isoflurane. The decrease in the CCP that occurred with isoflurane may have been the reason RMBF decreased in the LAD region where blood flow was collateral dependent. This decreased pressure gradient was due to a decreased proximal (aortic) pressure as the distal LAD pressure during LAD occlusion was the same with and without isoflurane. However, as RMBF in the normal zone did not differ with isoflurane from that in controls, there was no evidence that coronary blood flow was redistributed away from the ischemic zone. Most experiments in which redistribution of RMBF has been shown have included, in addition to a totally occluded coronary artery, a critical stenosis in the vessel supplying flow to the collateral bed. The effect of such a stenosis would be to amplify the reduction of proximal (aortic) perfusion pressure by further decreasing the pressure in the coronary artery distal to the stenosis where the collateral circulatory channels originate. However, the redistribution can occur without such a stenosis of the supply vessels to collateral channels (31). The endocardium is particularly vulnerable to such redistribution. In the present study the endo:epi RMBF ratio in the LAD area during LAD occlusion was not significantly different from that before occlusion with isoflurane, in contrast to the similar state without isoflurane (Table 5).

In the LAD zone during LAD occlusion O_2 supply decreased with isoflurane; O_2 consumption decreased to the same degree, so that the O_2 supply to consumption ratio was unaffected. This may imply that tissue oxygenation was not compromised further by the decreased RMBF seen with isoflurane, but the source of the decreased O_2 consumption during LAD occlusion with isoflurane is unclear. The decreased RMBF with isoflurane in the ischemic zone may have worsened its oxidative capability and decreased O_2 consumption. While overall myocardial O_2 consumption is decreased by isoflurane, a similar or enhanced effect in ischemic myocardium has not been documented.

The source of the marked hypercarbia during LAD occlusion in LAD venous blood (Table 7) is unclear. Because solubility of CO_2 in blood is inversely proportional to hydrogen ion concentration, some of the increase in P_{CO_2} in coronary venous blood was likely produced by a change in solubility, but not in content. Also, CO_2 production may be increased relative either to its elimination or to O_2 utilization. Early in the ischemic process, glycolysis is accelerated at a time when the tricarboxylic acid cycle is still active; thus CO_2 production would continue while decreased blood flow would impair CO_2 elimination. Oxidation of fatty acids is impaired by ischemia, tending to shift the respiratory quotient toward the carbohydrate value of 1.0. We have reported similar results in another investigation that specifically examined acid–base, electrolyte, and metabolic effects of early acute myocardial ischemia (32).

The coronary venous system has a less consistent epicardial pattern than that of the arterial system, so that samples of venous blood from the LAD companion vein may not contain blood only from the LAD perfusion zone. If the LADv blood samples we analyzed had been significantly contaminated by circumflex perfusion area blood, then the changes we observed during ischemia would have been proportionately smaller than the actual changes. The small contribution to the venous samples from areas with extremely small RMBF values (i.e., the central ischemic zone) would lead to the same underestimation. Areas with zero RMBF are not assessed by this technique. Using techniques similar to those reported here, one study has shown that the LAD companion vein contains blood predominately from the LAD perfusion area (33).

Thus, in this protocol, isoflurane administered during a 15-min period of LAD occlusion decreased CPP without changing distal LAD pressure. Other hemodynamic effects were relatively minor. Ischemic zone RMBF and O_2 supply were lower with isoflurane, but O_2 consumption was also lower; therefore, there was no change in O_2 utilization with isoflurane. Finally, the metabolic state of the ischemic myocardium as judged by coronary vencus (LAD) blood chemistry did not differ during LAD occlusion with or without isoflurane. We conclude, therefore, that isoflurane had no observed deleterious effects in this experimental model.

General Comments

The effect of isoflurane on the coronary circulation under normal conditions appears to be relatively straightforward: coronary vascular resistance decreases, overall coronary blood flow either is unaffected or increases, myocardial O_2 consumption decreases, and coronary venous O_2 content increases. The effects of isoflurane when coronary circulation is abnormal, as with one or more totally occluded or stenotic (or both) conductance vessels, are controversial. This controversy was highlighted by an editorial stating that isoflurane is "potentially dangerous" in patients with coronary artery disease because of its reported ability to induce coronary steal (26).

The basic concept of coronary steal is that a reduction of arterial smooth muscle tone in the coronary circulation will decrease blood flow resistance in normally perfused areas relative to the resistance in collateral dependent areas because, in the latter case, the vasodilator reserve has been exhausted (i.e., resistance is minimum and flow is pressure dependent) by the local metabolic needs of the myocardium. This produces a decrease in collateral perfusion pressure that can either cause or worsen ischemia in areas that depend on collateral flow. Importantly, for coronary steal to be invoked aortic perfusion pressure must be constant. Decreased perfusion pressure has the same net effect because autoregulation decreases coronary resistance in normally perfused areas to maintain flow until the decrease in pressure exceeds the autoregulatory range (CPP of approximately 40–50 mm Hg). Therefore, it is not plausible to attribute RMBF changes to "coronary steal" when aortic perfusion pressure is decreased (34).

In virtually all clinical studies and laboratory studies in which isoflurane has been associated with ischemic myocardial dysfunction or anaerobic metabolism, there has been a concomitant decrease in aortic pressure (11–14,35). In such circumstances, it is impossible to distinguish coronary vasodilation produced by isoflurane from that produced by decreased systemic pressure. Do other anesthetic agents that decrease arterial pressure also produce "ischemic" regional dysfunction in areas distal to cortical stenoses? The experimental data indicate that the answer is yes. For example, halothane, which is generally regarded to have little, if any, direct coronary vasodilating effect, can decrease arterial pressure and can produce ischemic dysfunction in myocardium that is perfused by a critically stenotic artery (36).

Other studies have shown a lack of deleterious effects of isoflurane in experimental models of myocardial ischemia. In swine, isoflurane is associated with a greater coronary reserve and a better preservation of cardiac function than halothane (37). In two studies using chronically instrumented dogs, all three volatile agents mildly decreased autoregulation (halothane < enflurane < isoflurane), but neither maximal coronary blood flow nor coronary reserve were affected (38,39). In another study, the hypotension associated with 1.7% end tidal isoflurane produced a significant decrease of the endo:epi ratio distal to a critical stenosis (40). The decrease remained despite restoration of proximal perfusion pressure with phenylephrine, but regional wall thickening was not significantly affected by the isoflurane, indicating that the reduced endocardial RMBF was still sufficient to avoid ischemic dysfunction. Alternation between halothane and isoflurane while measuring regional wall motion and blood flow distal to a critical stenosis and while maintaining proximal perfusion pressure constant, on the other hand, produced a consistent decrease in flow with isoflurane compared to halothane (41). These results are difficult to reconcile with the data reported here, although again, our data were gathered during total coronary occlusion. The rheology of flow across a critical stenosis is different from that associated with collateral flow into a collateral flow dependent area of myocardium.

Thus, the previously reported studies show that a decreased perfusion pressure produced by isoflurane may have adverse consequences for myocardium that is supplied by a critically stenosed coronary artery. However, whether isoflurane itself alters RMBF distribution (either regionally or transmurally) remains controversial. The results of this study show that in dogs, the extent of ischemic necrosis in myocardium after LAD occlusion is substantially decreased with isoflurane compared with control conditions. Despite this reduced infarct size, RMBF measurements did not differ between the groups. Measurements of regional myocardial metabolic variables after transient, total coronary artery occlusion showed that isoflurane was associated with a decreased LAD zone RMBF during LAD occlusion. The endo:epi RMBF ratio decreased during LAD occlusion in control conditions, but there was no significant change during isoflurane. We conclude that in this canine model of acute evolving myocardial infarction, isoflurane had no observed deleterious effect and was associated with salvage of myocardium.

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References

1. Tarhan S, Moffitt S, Moffitt EA, Taylor WF, Giuliani ER. Myocardial infarction after general anesthesia. JAMA 1972;220:1451–4.
2. Steen PA, Tinker JH, Tarhan S. Myocardial reinfarction after anesthesia and surgery. JAMA 1978;239:2566–70.
3. Mauney FM Jr, Ebert TA, Sabiston DC Jr. Postoperative myocardial infarction: a study of predisposing factors, diagnosis and mortality in a high risk group of surgical patients. Ann Surg 1970;172:497–503.
4. Roy WL, Edelist G, Gilbert B. Myocardial ischemia during non-cardiac surgical procedures in patients with coronary artery disease. Anesthesiology 1979;51:393–7.
5. Slogoff S, Keats AF. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107–14.
6. Slogoff S, Keats AF. Further observations on perioperative myocardial ischemia. Anesthesiology 1986;65:539.
7. Tarnow J, Eberlein HJ, Oser G. Influence of modern inhalation anesthetics on haemodynamics, myocardial contractility, left ventricular volumes and myocardial oxygen supply. Anaesthetist 1977;26:220–30.
8. Theye RA, Michenfelder JD. Individual organ contributions to the decrease in whole-body Vo_2 with isoflurane. Anesthesiology 1975;42:35–40.
9. Merin RG, Basch S. Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? Anesthesiology 1981;55:398–408.
10. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 1984;63:557–65.
11. Reiz S, Ostman M. Regional coronary hemodynamics during isoflurane-nitrous oxide anesthesia in patients with ischemic heart disease. Anesth Analg 1985;64:570–6.
12. Reiz S, Balfors E, Sorensen MB, Ariola S, Friedman A, Truedsson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983;59:91–7.
13. Moffitt EA, Barker RA, Glenn JJ, et al. Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary arterial surgery. Anesth Analg 1986;65:53–61.
14. Buffington GW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 1987;66:280–92.
15. Maroko PR, DeBoer LWV, Davis RF. Infarct size reduction: a critical review. Adv Cardiol 1979;27:289–316.

16. Bland JHL, Lowenstein E. Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology 1976;45:287–93.
17. Davis RF, DeBoer LWV, Rude RE, Lowenstein E, Maroko PR. The effect of halothane anesthesia on myocardial necrosis, hemodynamic performance, and regional myocardial blood flow in dogs following coronary artery occlusion. Anesthesiology 1983;59:402–11.
18. Davis RF, DeBoer LWV, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary occlusion in dogs. Anesth Analg 1986;65:711–7.
19. Yang SS, Bentivoglio LG, Maranhao V, Goldberg H. From Cardiac Catheterization Data to Hemodynamic Parameters. 3rd ed. Philadelphia: F.A. Davis, 1988.
20. Heymann MA, Bayne BD, Hoffman JIE, Rudolph AM. Blood flow measurements with radionuclide labeled particles. Prog Cardiovasc Dis 1977;20:55–79.
21. DeBoer LWV, Strauss HW, Kloner RA, et al. Autoradiographic method for measuring the ischemic myocardium at risk: effects of verapamil on infarct size after experimental coronary artery occlusion. Proc Natl Acad Sci, USA 1980;77:6119–23.
22. Lie JT, Paiolero PC, Holley KE, Titus JL. Macroscopic enzyme-mapping verification of large, homogeneous, experimental myocardial infarcts of predictable size and location in dogs. J Thorac Cardiovasc Surg 1975;69:599–605.
23. Sidi A, Rush W, Davis RF. Direct cannulation of myocardial blood vessels without interfering with regional blood flow distribution, resting blood flow or reactive hyperemia. J Cardiothorac Anesth 1989;3:78–83.
24. Maroko PR, Kjekshus JK, Sobel BE. Factors influencing infarct size following experimental coronary artery occlusions. Circulation 1971;43:67–82.
25. Muller JE, Maroko PR, Braunwald E. Evaluation of precordial electrocardiographic mapping as a means of assessing changes in myocardial ischemic injury. Circulation 1975;52:16–27.
26. Kates RA, Stack RS, Hill RF. General anesthesia for patients undergoing percutaneous transluminal coronary angioplasty during acute myocardial infarction. Anesth Analg 1986;65: 815–8.
27. Becker LC. Is isoflurane dangerous for the patient with coronary artery disease? Anesthesiology 1987;66:259–61.
28. Fishbein M. The pathology of myocardial infarction. In: Cohn LH, ed. The Treatment of Acute Myocardial Ischemia: An Integrated Medical/Surgical Approach. New York: Futura Publishing Company, Inc., 1979:15–24.
29. Gottlieb GJ, Kubo SH, Alonso DR. Ultrastructural characterization of the border zone surrounding early experimental myocardial infarcts in dogs. Am J Pathol 1981;103:292–303.
30. Vivaldi MT, Kloner RA, Schoen FJ. Triphenyltetrazolium staining of irreversible ischemic injury following coronary artery occlusion in rats. Am J Pathol 1985;121:522–30.
31. Patterson RE, Kirk ES. Coronary steal mechanisms in dogs with one-vessel occlusion and other arteries normal. Circulation 1983;67:1009–15.
32. Sidi A, Rush W, Davis RF. Regional myocardial metabolism and electrolyte balance during acute ischemia in dogs. J Cardiothorac Anesth 1988;2:650–7.
33. Vinten-Johansen J, Johnston WE, Crystal GJ. Validation of local venous sampling within the at risk left anterior descending artery vascular bed in the canine left ventricle. Cardiovasc Res 1987;21:646–51.
34. Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 1978;57: 1101–10.
35. Priebe HJ, Foex P. Isoflurane causes regional myocardial dysfunction in dogs with critical coronary artery stenoses. Anesthesiology 1987;66:293–300.
36. Lowenstein E, Foex P, Francis CM, Davies WL, Yusuf S, Ryder WA. Regional ischemic ventricular dysfunction in myocardium supplied by a narrowed coronary artery with increasing halothane concentration in the dog. Anesthesiology 1981;55: 349–59.
37. Gilbert M, Roberts SL, Mori M, Blomberg R, Tinker JH. Comparative coronary vascular reactivity and hemodynamics during halothane and isoflurane anesthesia in swine. Anesthesiology 1988;68:243–53.
38. Hickey RF, Sybert PE, Verrier ED, Cason BA. Effects of halothane, enflurane, and isoflurane on coronary blood flow autoregulation and coronary vascular reserve in the canine heart. Anesthesiology 1988;68:21–30.
39. Cason BA, Verrier ED, London MJ, Mangano DT, Hickey RF. Effects of isoflurane and halothane on coronary vascular resistance and collateral myocardial blood flow: their capacity to induce coronary steal. Anesthesiology 1987;67:665–75.
40. Tatekawa S, Traber KB, Hantler CB, Tait AR, Gallagher KP, Knight PR. Effects of isoflurane on myocardial blood flow, function, and oxygen consumption in the presence of critical coronary stenosis in dogs. Anesth Analg 1987;66:1073–82.
41. Priebe HJ. Isoflurane causes more severe regional myocardial dysfunction than halothane in dogs with a critical coronary artery stenosis. Anesthesiology 1988;69:72–83.

ANESTH ANALG 587
1989;69:587–92

Role of Spinal Adenosine Receptors in Modulating the Hyperesthesia Produced by Spinal Glycine Receptor Antagonism

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SOSNOWSKI M, YAKSH TL. Role of spinal adenosine receptors in modulating the hyperesthesia produced by spinal glycine receptor antagonism. Anesth Analg 1989;69:587–92.

The intrathecal administration of strychnine in rats yields a prominent touch-evoked allodynia. The effects of an intrathecally administered A_1 adenosine agonist: N^6-(L-2-phenylisopropyl)-adenosine (LPIA) or an A_2 adenosine agonist: 5′-(N-ethyl carboxamido)-adenosine (NECA), on this touch-evoked hyperesthesia were examined. Over the range of 0.3–1.0 nmol these agents produced a dose-dependent inhibition of the strychnine-evoked hyperesthesia. This inhibition was reversed following intraperitoneal injection of caffeine, an adenosine receptor antagonist. No statistical differences between LPIA and NECA were recorded. The powerful effect of adenosine analogues on strychnine hyperesthesia occur at doses that have only a mild analgesic effect on the thermally evoked hot-plate response. This effect is in contrast to opioids, which have been reported to be only minimally effective against strychnine-evoked hyperesthesia. The characteristics of the strychnine hyperesthesia appear to mimic the clinical phenomenon observed in patients suffering from sensory dysesthesia following nerve injury and suggest a possible role for the adenosine receptor in certain pain states.

Key Words: PAIN, SPINAL CORD PAIN RECEPTORS.
RECEPTORS, SPINAL CORD PAIN RECEPTORS.
SPINAL CORD, PAIN RECEPTORS.

A variety of spinal cord receptors modify the response to noxious visceral and somatic stimuli, i.e., produce analgesia. One property of this modulation is that it appears selectively directed at the input generated by high-threshold thermal, mechanical, and chemical stimuli that activate certain populations of A_δ and C fibers. Input evoked by low-threshold stimuli (i.e., brush, touch, proprioception) does not appear to be affected. This selective modulation is thought to result from the association of several receptor types (μ, δ, and α_2 for example), with the spinal systems processing these types of information (For review and references, see Ref. 1).

It is clear, however, that a "pain state" can also be induced in the absence of activity in small afferents. Thus, following nerve injury, dysesthetic states may be evoked by activity with low-threshold stimuli that activate A_β afferents (2). One characteristic of these clinical syndromes is their relative refractoriness to opioids (3). This observation suggests that the pharmacology of the system activated in these pathologic states may differ from that activated under norma circumstances by high-threshold afferents.

Recent studies have suggested that inhibition of spinal glycine receptors by the intrathecal administration of low doses of strychnine will yield an anima model in which innocuous mechanical stimuli (touch) results in a prominent pain behavior (allodynia). This allodynia appears to be only partially antagonized by high doses of spinal opioids (4).

A growing body of information has begun to emphasize the role of purine receptors in modulating afferent processing in the dorsal horn (5,6). Adenosine, a probable purinergic agonist, has been suggested to exert its effect at specific purine receptor sites. Recently, such purine receptors have been classified into two major subtypes based on their ability (after activation) to inhibit (A_1) or stimulate (A_2) adenylate cyclase (7). Methylxanthines (e.g., caffeine) are known to antagonize with similar potencies the two types of receptors (8). The purpose of this study was to investigate the possibility that the exaggerated response to the light-touch stimulus evoked by glycine inhibition might be sensitive to spinal A_1 or A_2 receptor agonist activity.

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Materials and Methods

Animal Preparation

Experiments were performed in male Sprague-Dawley rats (250–300 g). In each experiment, except the saline group ($n = 16$), four rats were used for each data point and no rat was injected more than once. This study received prior institutional review board approval for animal research. Catheterization of the subarachnoid space was as described previously (9). Under halothane anesthesia, through an incision in the atlanto-occipital membrane, a PE-10 catheter was advanced 8 cm caudally to position its tip at the level of the lumbar enlargement. The catheter was externalized on top of the skull and the incision sealed with a piece of steel wire. The wound was then closed with silk sutures.

Measurement of Allodynia

To induce hyperesthesia-allodynia, strychnine (30 μg/3 μL) was given intrathecally. This has been shown (4,10) to result immediately (less than 1-min latency) in a syndrome characterized first by intermittent bouts of spontaneous agitation (SA) in which the rat bites and scratches at its flanks at levels corresponding to the dermatomes where the tip of the catheter lies (T_{12}–L_1). During intervening periods, the animal sits quietly, but a prominent agitation response can be readily evoked by a nonnoxious tactile stimulation (e.g., a probe drawn lightly across the flank: touch-evoked agitation [TEA]). To quantify SA in this study, a three-point rating scale was employed: 0 = no change, 1 = mild squeaking, 2 = vigorous squeaking accompanied by biting and scratching the tactile probe. To assess TEA, a three-point scale was also used: 0 = no effect of stroking, 1 = mild squeaking with attempts to move away from the probe that lightly strokes the fur, 2 = vigorous squeaking evoked by the stroking probe with biting and strong efforts to escape. During the 50 min following injection each animal was assigned an SA score for every minute during the first 30 min, and then every 5 min for the remaining 20 min. Similarly, during quiescent periods, a TEA score was assigned at 5-min intervals for the entire 50-min period. This protocol has been described extensively elsewhere (4). Animals were sacrificed immediately at the end of the 50-min observation period.

Drug Injections and Treatment Groups

Drugs administered intrathecally were LPIA [N^6-(L-2-phenylisopropyl)-adenosine; Sigma]; NECA [5′-(N-ethylcarboxamido-adenosine); Sigma]; strychnine sulfate (Sigma); and caffeine (Sigma). NECA and LPIA were mixed such that all doses were administered in a 10-μL solution followed by 10-μL sodium chloride (0.9%) vehicle to flush the catheter. Each control animal received an intrathecal injection of equal volumes of saline. To minimize spinal redistribution, strychnine was injected intrathecally in a 3-μL solution (30 μg) followed by a 10-μL sodium chloride (0.9%) vehicle. The adenosine analogue was given 10 min before strychnine. The dose-response curves were made up, using three doses of NECA and LPIA (0.1, 0.3, 1.0 mmol). To examine its ability to antagonize LPIA or NECA (1.0 nmol), caffeine was administered intraperitoneally (600 μmol in 300 μL) just before intrathecal strychnine.

Statistics

To compare the antiallodynic effects of the agents, the scores assessed over the 50-min period were cumulated and expressed as a percent of the maximum possible score. Thus, the maximum possible scores for TEA and SA were 20 and 68, respectively. Comparisons were made using analysis of variance (ANOVA). Statistical significance ($P < 0.05$) was further examined with a Newman–Keul test for multiple comparison.

Results

Effects of the Intrathecal Administration of Adenosine Analogues on Hyperesthesia and Allodynia

Within 1 min of the intrathecal administration of strychnine (30 μg), prominent SA was observed (see Figure 1). This SA was interspaced with frequent periods of quiescent behavior. In these periods, light stroking of the flanks resulted in vigorous squeaking and strong avoidance/escape behavior (TEA). As shown in Figures 1 and 2, intrathecal LPIA and NECA at 1.0 nmol resulted in an equal and significant suppression of both SA and TEA. This attenuating effect of the intrathecal purinergic agonist was dose dependent (Figure 2). As indicated, the effect on TEA was particularly pronounced as at 0.3 nmol both analogues could still evoke a significant suppression by either analogue of this evoked behavior.

Pretreatment with intraperitoneal caffeine (600 μmol) alone resulted in a small enhancement of the SA (Figure 3, top) and TEA scores (Figure 3, bottom). Such pretreatment with intraperitoneal caffeine (600

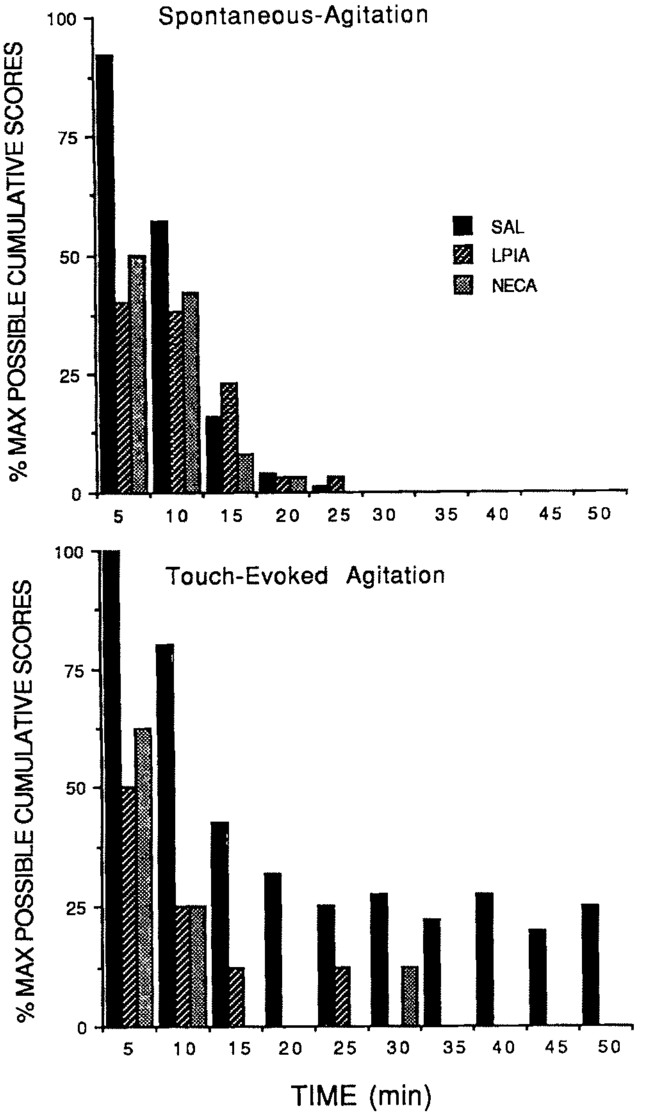

Figure 1. Time-course for the effect of intrathecal, saline (SAL), NECA, and LPIA at 1.0 nmol on spontaneous agitation (top) and touch-evoked hyperesthesia (bottom) following intrathecal strychnine. Each column represents the percent of the maximum possible cumulative scores of 16 rats for saline and four rats for LPIA and NECA evaluated every minute (spontaneous agitation) or every 5 min (touch-evoked agitation).

μmol) completely reversed the antiallodynic effects of intrathecal LPIA or NECA (Figure 3).

Discussion

Strychnine-Evoked Allodynia

Following intrathecal administration of strychnine, the animals begin to bite and/or scratch the dermatomes affected by the injection. This behavior can be evoked by a light, clearly low-threshold brush of the pelage and has been shown to result in a stimulus-dependent increase in blood pressure (4). Previous reports have shown that intrathecal strychnine has little detectable influence on the animal's response to noxious thermal stimuli (10). These behavioral observations are in accord with the electrophysiological findings made following the application of strychnine onto the spinal cord. In those experiments, the response of dorsal-horn wide dynamic range neurons to low-threshold, tactile stimuli were significantly facilitated by glycine inhibition (11). Similar experiments, carried out with iontophoretically administered strychnine, also demonstrated a marked facilitation of the postsynaptic discharge evoked by afferent input and enlarged the receptive fields for nonnoxious mechanical stimulation (12).

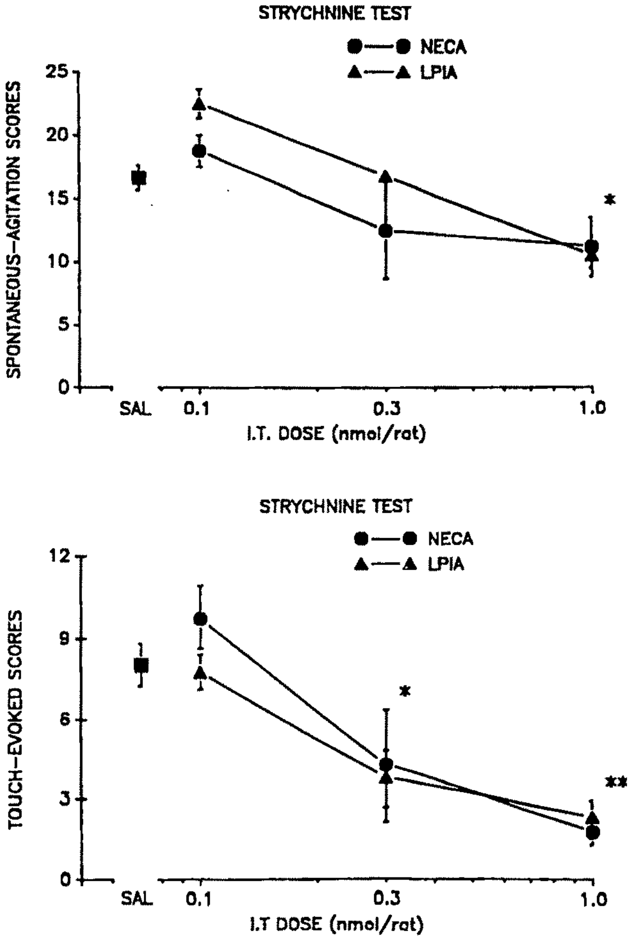

Figure 2. Log dose-response curves for the effect of adenosine analogues on the spontaneous agitation (top) and touch-evoked agitation (bottom) tests evoked following intrathecal strychnine (I.T.). Each point represents the mean ± SEM of four rats. $^*P < 0.05$ as compared to saline (SAL) treated group.

Strychnine interacts with high affinity at glycine receptor sites that are found in lamina II, III, and V of the dorsal horn (13). Glycine receptors have been implicated in the late depressant effect caused by electrical stimulation of low-threshold primary af-

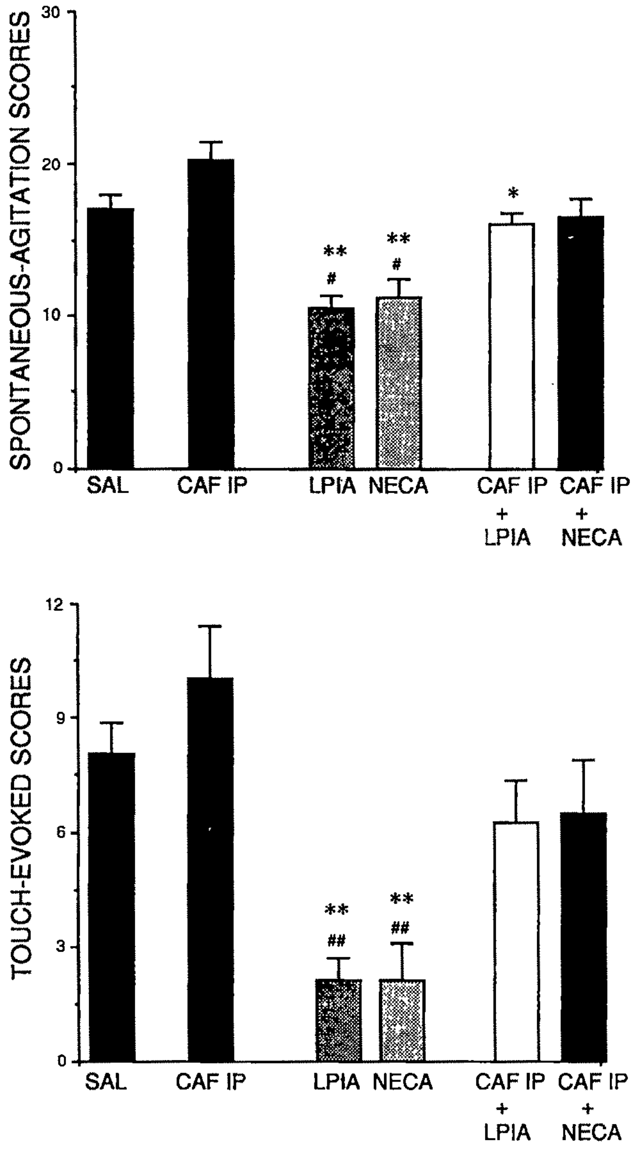

Figure 3. Effect of intrathecal NECA and LPIA at 1 nmol/rat alone and with pretreatment of intraperitoneal (I.P.) caffeine (CAF) (600 μmol) on the spontaneous agitation (top) and touch-evoked hyperesthesia (bottom) following intrathecal injection of strychnine 30 μg. Columns are mean ± SEM of four rats for NECA, LPIA, and caffeine-treated groups and 16 rats for saline (SAL). $^*P < 0.05$, $^{**}P < 0.01$ as compared to caffeine-treated animals. $\#P < 0.05$, $\#\#P < 0.01$ as compared to saline (SAL) treated animals.

ferent fibers (14). These afferents terminate in Rexed lamina IV and V. This suggests that tactile stimulation mediated by A_β fibers, a type of stimulation not routinely thought to be painful, may activate local glycine inhibition. This inhibition then subsequently regulates the discharge evoked by the low-threshold afferent itself.

Although the precise mechanism of the allodynia evoked by spinal strychnine is not known, it is clear that the resulting pain behavior is mediated by a mechanism distinct from those substrates activated by high intensity, potentially tissue-damaging stimuli. First, activation of a low-threshold mechanoreceptor is an adequate stimulus. Second, the behavior has a clearly distinctive pharmacology. Thus, while μ, δ, and α_2 agonists yield a powerful suppression of the response to somatic and visceral nociceptive stimuli, they show surprisingly little effect on TEA (4). In contrast, both adenosine-receptor agonists that have only a mild effect upon thermal nociception (15), and glutamate receptor antagonists of the N-methyl D-asparatate (NMDA) type that have no detectable effect upon thermal nociception (4) yield a powerful blockade of the TEA response. This reversal of the structure–activity relationship is strong evidence for differences in the substrates mediating the pain behavior evoked by high-threshold somatic stimuli in the normal animal and by low-threshold mechanoreceptors in the strychnine-treated animal.

Mechanism of Adenosine Action

The fact that adenosine analogues dramatically reduced the behavior induced by intrathecal strychnine must be emphasized, as it occurs at doses that demonstrated only mild antinociceptive properties on the hot-plate and tail-flick tests and did not yield motor impairment (15). Two mechanisms are hypothesized.

1) The allodynia phenomena results from a loss of local inhibition on A_β-evoked activity, and this may result in an exaggerated postsynaptic discharge, perhaps inducing local seizurelike activity. Importantly, spinal agents such as substance P (sP) or high doses of morphine (or low doses of the 3-glucuronide conjugate) can evoke a similar phenomena (16–19). These effects are antagonized by anticonvulsants such as valproic acid or chlordiazepoxide (16). Importantly, adenosine analogues have also been shown to be potent anticonvulsants (20–23). Adenosine impedes seizure spread and seizure continuation (but not initiation) in the kindling model of epilepsy (21). Conversely, methylxanthine prolongs those seizures (21). A synergistic action between carbamazepine and LPIA has been observed in caffeine and in pentylenetetrazole-induced convulsions (23), even though carbamazepine treatment in vivo appears to up-regulate adenosine receptors (24).

2) As noted previously, the strychnine-evoked hyperesthesia is readily antagonized by glutamate receptor antagonists, suggesting a possible association of a dorsal-horn glutamate system in this dysesthesia. Adenosine has been shown to inhibit glutamate release in the hippocampal slice (25) and dentate gyrus (26). This effect appears to involve an

A_1 receptor, as the effect is abolished by 8-phenyltheophylline and pertussis toxin. A selective presynaptic inhibition of glutamate release (compared to a postsynaptic effect that modulates afferent outflow) is a possible explanation. However, recent studies in spinal conditions have not shown A_1 or A_2 binding on primary afferents (27). This suggests that adenosine may interact with the release of glutamate from small dorsal-horn interneurons.

Clinical Correlates

The potent effect of a spinal adenosine receptor on pain states evoked in abnormal circumstances suggests that this receptor system may also play a role in normal circumstances. Salter and Henry (28) observed that the depressant effect on nociceptive neurons in the dorsal horn, observed following vibrations applied to the ipsilateral hind limb, could be potentiated by an adenosine uptake inhibitor (dipyramidole) and reversed by caffeine, and was unaffected by naloxone. They proposed that the analgesic effect of vibration is mediated at the spinal level by purinergic receptors. This is consistent with the clinical application of the gate-control theory (29) that leads to the use of a transcutaneous electrical nerve stimulator. Such stimulation activates large primary afferents and produces analgesia in the area affected by the cutaneous vibration. Conversely, in the inherited nervous system disorder, the Lesh–Nyhan syndrome, an affected child shows involuntary movement and a self-injurious behavior, often seen as destructive biting of lips and fingers. This syndrome is associated with the enzyme hypoxanthine-guanine phosphoribosyl transferase that leads to lower plasma concentration of adenosine. Caffeine worsens this syndrome (30). Whether this syndrome is reflected by a central adenosine disorder is not known.

In summary, our study supports the theory that certain pain syndromes may involve physiological and pharmacological substrates that distinctly differ from those activated in the spinal cord by somatic and visceral stimuli. These differences may account for the putative lack of effect of drugs acting upon receptors modulating small afferent input (such as opioids and α_2 agonists) and provide some degree of scientific support for the use of agents that do not routinely alter somatic pain processing. Thus, in the context of the present studies, nortriptyline has been employed in certain types of chronic pain because of its antidepressive properties (31). We also know that this agent is a potent inhibitor of adenosine uptake (32).

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References

1. Yaksh TL, Aimone L. The central pharmacology of pain transmission. In: Wall PD, Melzack R, eds. Textbook of Pain. Edinburgh: Churchill Livingstone, 1989:283–320.
2. Campbell JN, Raja SN, Meyer RA, MacKinnon SE. Myelinated afferents signal the hyperalgesia associated with nerve injury. Pain 1988;32:89–94.
3. Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. Pain 1988;33:11–23.
4. Yaksh TL. Behavioral and autonomic correlates of the tactile evoked allodynia produced by spinal glycine inhibition effects of modulatory receptor systems and excitatory amino acid antagonists. Pain 1989;32:111–23.
5. Sawynok J, Sweeney MI, White TD. Classification of adenosine receptors mediating antinociception in the rat spinal cord. Br J Pharmacol 1986;88:923–30.
6. DeLander GE, Hopkins CJ. Spinal adenosine modulates descending antinociceptive pathways stimulated by morphine. J Pharmacol Exp Ther 1986;239:88–93.
7. Van Calker P, Muller M, Hamprecht B. Adenosine regulates via two different types of receptors the accumulation of cAMP in cultured brain cells. J Neurochem 1979;33:999–1005.
8. Daly JW, Bruno RF, Snyder SH. Adenosine receptors in the central nervous system: relationship to the central action of methylxanthines. Life Sci 1981;28:2083–97.
9. Yaksh TL, Rudy TA. Chronic catheterization of the spinal subarachnoid space. Physiol Behav 1976;17:1031–6.
10. Beyer C, Roberts LA, Komisaruk BR. Hyperalgesia induced by altered glycinergic activity at the spinal cord. Life Sci 1985; 37:875–82.
11. Khayyat GF, Yu YJ, King RB. Response patterns to noxious and non-noxious stimuli in rostral trigeminal relay nuclei. Brain Res 1975;97:47–60.
12. Zieglgansberger W, Herz A. Changes of cutaneous receptive fields of spino-cervical tract neurons and other dorsal horn neurons by microelectrophoretically administered amino acids. Exp Brain Res 1971;13:111–26.
13. Zarbin MA, Wamsley JK, Kuhar MJ. Glycine receptor: light microscopic autoradiographic localization with [^{3}H] strychnine. J Neurosci 1981;1:532–47.
14. Game CJA, Lodge D. The pharmacology of the inhibition of dorsal horn neurons by impulses in myelinated cutaneous afferents in the cat. Exp Brain Res 1975;23:75–84.
15. Sosnowski M, Stevens CW, Yaksh TL. Assessment of the role of A_1/A_2 adenosine receptors mediating the purine antinociception, motor and autonomic function in the rat spinal cord. J Pharmacol Exp Ther (in press).
16. Frenk H, Bossut D, Mayer DJ. Is substance P a primary afferent neurotransmitter for nociceptive input? II. Valproic acid and chlordiadepoxide decrease behaviors elicited by intrathecal injection of substance P and excitatory compounds. Brain Res 1988;455:240–6.
17. Frenk H. Pro and anticonvulsant actions of morphine and the endogenous opioids: involvement and interpretations of multiple opiate and nonopiate systems. Brain Res Rev 1983; 6:197–210.
18. Yaksh TL, Harty GL, Onofrio BM. High doses of spinal morphine produce a nonopiate receptor mediated hyperesthe-

sia: Clinical and theoretic implications. Anesthesiology 1986; 64:590–7.

19. Yaksh TL, Harty GJ. Pharmacology of the allodynia in rats evoked by high dose intrathecal morphine. J Pharmacol Exp Ther 1988;244:501–7.
20. Dunwiddie TW, Worth T. Sedative and anticonvulsant effects of adenosine analogs in mouse and rat. J Pharmacol Exp Ther 1982;220:70–6.
21. Dragunow M, Goffard GV, Laverty R. Is adenosine an endogenous anticonvulsant? Epilepsia 1985;26:480–7.
22. Frenk H, Watkins LR, Mayer DJ. Differential behavior effects induced by intrathecal microinjection of opiates: comparison of convulsive and cataleptic effects produced by morphine, methadone and D-ala^{2}methionine-enkephalinamide. Brain Res 1984;299:31–42.
23. Popoli P, Benedetti M, Scotti de Carolis A. Anticonvulsant activity of carbamazepine and N^6-L-phenylisopropyladenosine in rabbits. Relationship to adenosine receptors in central nervous system. Pharmacol Biochem Behav 1988;29:533–9.
24. Marangos PJ, Weiss SRB, Montgomery P, Patel J, Narang PK, Cappabianca AM, Post RM. Chronic carbamazepine treatment increases brain adenosine receptors. Epilepsia 1985;26:493–8.
25. Fastbom J, Fredholm BB. Inhibition of $[^3H]$ glutamate release from rat hippocampal slices by L-phenylisopropyladenosine. Acta Physiol Scand 1985;125:121–3.
26. Dolphin AC, Prestwich SA. Pertussin toxin reverses adenosine inhibition of neuronal glutamate release. Nature 1985; 316:148–50.
27. Choco JI, Green RD, Proudfit HK. Adenosine A_1 and A_2 receptors of the substantia gelatinosa are located predominantly on intrinsic neurons: an autoradiography study. J Pharmacol Exp Ther 1988;247:757–64.
28. Salter MW, Henry JL. Evidence that adenosine mediates the depression spinal dorsal horn neurons induced by peripheral vibration in the cat. Neuroscience 1987;22:631–50.
29. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150:971–80.
30. Stone TW. Physiological roles for adenosine and adenosine 5′-triphosphate in the nervous system. Neuroscience 1981;6:523–55.
31. Walsh TD. Antidepressants in chronic pain. Clin Neuropharmacol 1983;6(4):271–95.
32. Phillis JW, Wu PH. The effect of various centrally active drugs on adenosine uptake by the central nervous system. Comp Biochem Physiol 1982;72C:179–87.

Spinal Anesthesia with Plain Bupivacaine 0.5%: Regression of Sensory and Motor Blockade with Different Temperatures of the Anesthetic Solution

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STIENSTRA R, GIELEN M, VAN POORTEN F, KROON JW. Spinal anesthesia with plain bupivacaine 0.5%: regression of sensory and motor blockade with different temperatures of the anesthetic solution. Anesth Analg 1989;69:593–7.

*Onset (defined as the time between injection and achievement of the highest level of sensory blockade), duration, and regression of sensory and motor blockade after the intrathecal administration of 3 mL plain bupivacaine 0.5%, previously equilibrated to either 37°C or 20°C, were studied in two groups of 20 patients. In patients receiving the solution equilibrated to 37°C, the maximum level of sensory blockade was significantly higher (T 4.6 vs T 7.5), variability was smaller (*SEM *0.33 vs 0.58), and duration of the sensory level of blockade at or above T 6, T 8, and T 10 was significantly longer (56 min vs 20 min, 101 min vs 59 min, and 131 min vs 77 min, respectively). There were no significant differences with regard to onset of sensory and motor blockade or either the time needed both for the sensory level of blockade to regress two segments from its highest level and to the first lumbar segment, or the duration of complete motor blockade of the lower limbs. It is concluded that the intrathecal administration of a bupivacaine solution previously equilibrated to 37°C as compared with a solution injected at room temperature results in a higher, more predictable maximum sensory level of blockade with longer duration at or above T 6, T 8, and T 10.*

Key Words: ANESTHETIC TECHNIQUES, SPINAL. ANESTHETICS, LOCAL—bupivacaine.

The plain solution of bupivacaine 0.5% has been established as a useful local anesthetic agent for spinal anesthesia (1–5), although the predictability of the maximum level of sensory analgesia is reported to be poor (6–15). As it has been shown that keeping the patients seated for 2.5 min after intrathecal injection increases cephalad spread (16), satisfactory high levels of sensory blockade have been reported (16–21). Recently we demonstrated that equilibrating the bupivacaine solution to 37°C before injection results in a higher and more predictable level of maximum cephalad spread (22). The present study was undertaken to compare the onset, duration, and regression of sensory and motor blockade when using the plain solution of bupivacaine 0.5% previously equilibrated to either 37°C or 20°C.

Patients and Methods

Forty male patients (ASA physical status I–II) scheduled for urologic surgery were randomly allocated to one of two groups, each group comprising 20 patients. All patients received 3 mL plain bupivacaine 0.5% while they were in the sitting position. The sitting position was maintained for 3 min after completion of the intrathecal injection, after which the patients were placed in the supine horizontal position. Dural puncture was performed at the L3–L4 interspace using a midline or paramedian approach and a 25-gauge spinal needle. The bupivacaine solution was injected at a rate of 0.2 mL/sec. Patients in group 1 received a solution that had previously been equilibrated to 37°C for at least 24 hr. Patients in group 2 received a solution that had been equilibrated to 20°C for at least 24 hr. Syringes used to administer

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Table 1. Characteristics of the Patients Studied

	Group 1 (*n* = 20)	Group 2 (*n* = 20)	Delta 1–2 (*P*-value)
Age (years)	66 ± 1.85	71 ± 1.62	NS
Height (cm)	174 ± 1.45	173 ± 1.30	NS
Weight (kg)	78 ± 1.84	74 ± 2.05	NS

Group 1: plain bupivacaine, 37°C. Group 2: plain bupivacaine, 20°C.
NS, no statistically significant differences.
Data are means ± SEM.

Table 2. Onset and Regression of Motor Blockade and Maximum Level of Sensory Blockade

	Group 1 (*n* = 20)	Group 2 (*n* = 20)	Delta 1–2 (*P*-value)
Analgesia onset (min)	21.0 ± 1.43	23.5 ± 2.18	NS
Maximum block	T 4.6 ± 0.33	T 7.5 ± 0.58	<0.001
2 S regression (min)	61 ± 5.4	79 ± 7.2	NS
L 1 regression (min)	167 ± 7.2	156 ± 9.8	NS
Motor blockade onset (min)	13 ± 1.3	14 ± 1.3	NS
Motor blockade regression Bromage 3→2 (min)	151 ± 9.6	159 ± 8.1	NS

Groups as defined in Table 1. Analgesia onset: average time from injection to maximum level of sensory blockade. Maximum block: average maximum level of sensory blockade as measured by pinprick. 2 S regression: time between achievement of the highest level of sensory blockade and its regression to a level two segments lower. L 1 regression, time between achievement of the highest level of sensory blockade and its regression to the first lumbar segment. Motor blockade onset: average time from injection to complete motor blockade of the lower limbs (Bromage 3). Motor blockade regression Bromage 3→2: average time from achievement of complete motor blockade of the lower limbs (Bromage 3) to the ability to move the feet (Bromage 2).
NS: no statistically significant differences.
Data are means ± SEM.

the bupivacaine solution were also equilibrated to 37°C and 20°C, respectively. The study was approved by the Ethics Committee of our institution and informed consent was obtained from all patients.

Premedication consisted of lorazepam 1 mg orally the night before surgery. Before the institution of spinal anesthesia, 500 mL of Ringer's solution was administered by rapid intravenous infusion, followed, after completion of the intrathecal injection, by 500 mL of a plasma expander (Haemaccel) at a slower rate. Using an automatic cycling device, blood pressure and pulse rate were measured before injection and at 5-min intervals after injection until the patients were returned to the ward. ECG was monitored continuously.

Measurement of the level of sensory changes was made at 10-min intervals during the first 30 min and at 15-min intervals thereafter until regression to the first lumbar segment. Sensory loss was measured in the anterior axillary line using a short bevelled 25-gauge needle. The segment at which there was loss of sensation to pinprick was recorded. For comparisons, the average levels of sensory blockade after 10, 20, 30, 60, and 120 min were used. Motor blockade of the lower limbs was assessed using a 0–3 scale as described by Bromage (23) at the same intervals as the measurements of the level of sensory changes until regression from 3 to 2 on the Bromage scale.

All inductions of spinal anesthesia were made by the authors (RS and FvP); all observations were made by one author (JWK) under "observer blind" conditions. Results are expressed as means ± SEM. Statistical analysis used the Mann–Whitney U test for intergroup comparisons. $P \leq 0.05$ was taken indicative of statistically significant differences.

Results

There were no statistically significant differences between the two groups with respect to age, height, and weight (Table 1). The onset of sensory blockade, defined as the time between injection and achievement of the highest level of sensory blockade, averaged 21.0 min in group 1 and 23.5 min in group 2, the difference not being statistically significant. The sensory level of blockade averaged T 4.6 (range: T2–T7) in group 1 and T 7.5 (range: T3–T12) in group 2; this difference was statistically significant. The average levels of sensory blockade remained significantly higher in group 1 at all times (10, 20, 30, 60, and 120 min after injection). Two-segment regression, defined as the time between achievement of the highest level of sensory blockade and its regression to a level two segments lower, averaged 61 min in group 1 and 79 min in group 2; this difference was not statistically significant. Regression to L1, defined as the time between achievement of the highest level of sensory blockade and its regression to the first lumbar segment, averaged 167 min in group 1 and 156 min in group 2, the difference not being statistically significant. All patients had complete motor blockade of the lower limbs after 30 min. The onset of complete motor blockade of the lower limbs averaged 13 min in group 1 and 14 min in group 2; the difference was statistically not significant. Regression of motor blockade from 3 to 2 on the scale of Bromage took 151 min in group 1 and 159 min in group 2, a difference that was not statistically significant.

The data on onset, level of sensory blockade, and regression are shown in Table 2. The regression of the sensory level of blockade as a function of time is shown in Figure 1. Figure 2 shows the durations of sensory blockade at or above T 10, T 8, and T 6, which were, respectively, 131 min, 101 min, and 56 min in group 1 and 77 min, 59 min, and 20 min in group 2;

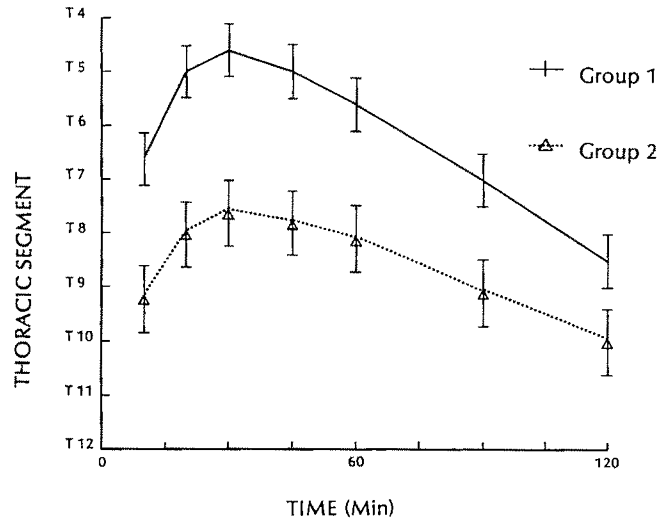

Figure 1. Regression of the average sensory levels of blockade as a function of time. The horizontal axis shows the time in minutes after intrathecal injection of 3 mL plain bupivacaine 0.5%; the vertical axis shows the average thoracic segment at which loss of sensation to pinprick was measured. Vertical bars represent SEM. The differences between the two groups, which were compared at 10, 20, 30, 60, and 120 min, were significant. Group 1: plain bupivacaine, 37°C. Group 2: plain bupivacaine, 20°C.

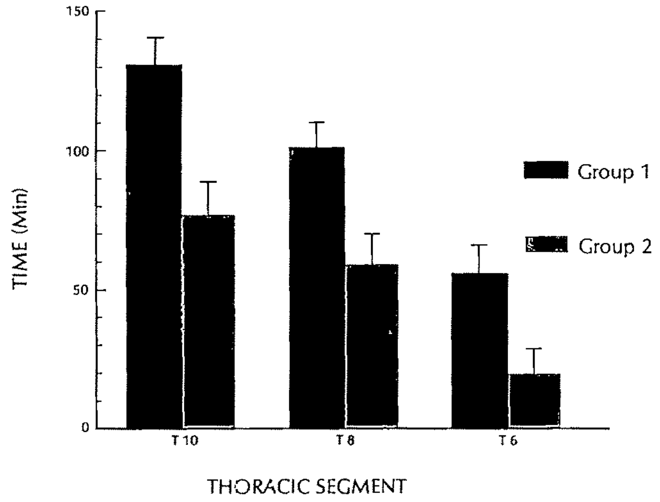

Figure 2. Average duration of sensory blockade at or above T 10, T 8, and T 6. The horizontal axis shows the thoracic segment; the vertical axis shows the time interval in minutes from the first to the last measurement at which the sensory level of blockade as determined by pinprick was at or above the specified thoracic segment. Vertical bars represent SEM. The differences between the two groups in duration of sensory blockade at or above T 10, T 8, and T 6 were significant. Group 1: plain bupivacaine, 37°C. Group 2: plain bupivacaine, 20°C.

these differences were statistically significant. Figure 3 shows the number of patients with a sensory level of blockade at or above T 10 as a function of time.

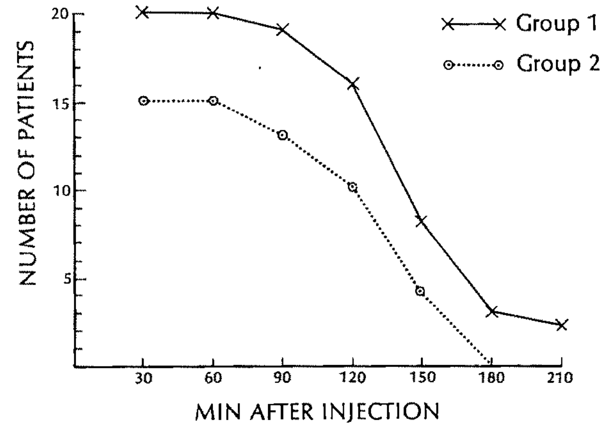

Figure 3. The number of patients with a sensory level of blockade as determined by pinprick at or above T 10 as a function of time after injection. The horizontal axis shows the time in minutes after intrathecal injection of 3 mL plain bupivacaine 0.5%; the vertical axis shows the number of patients with a level of sensory blockade at or above T 10. Group 1: plain bupivacaine, 37°C. Group 2: plain bupivacaine, 20°C.

Baseline systolic blood pressures and heart rates were similar in the two groups. Systolic blood pressures decreased in both groups, decreases being more pronounced in group 1. In five patients in group 1 and in one patient in group 2 the decrease in blood pressure necessitated the administration of ephedrine (15 mg intravenously plus 35 mg intramuscularly).

In group 1, three patients were given 0.5 mg alfentanil intravenously during surgery: in one of the three the level of sensory blockade at the time (120 min after intrathecal injection) was at T 12; the two other patients experienced pain (one during manipulation of the peritoneum in the inguinal region, the other during traction on the spermatic cord) while the level of sensory blockade was at T 7 (105 and 140 min after intrathecal injection). In group 2, one patient was given 0.5 mg alfentanil intravenously during surgery because of pain at a time when the level of sensory blockade was T 12 (75 min after intrathecal injection). In none of these patients were other or repeated analgetics necessary.

One patient (group 1, 67 years) suffered from postspinal headache, which was successfully treated with an epidural blood patch after 3 days.

Discussion

That many factors affect the intrathecal spread of local anesthetic solutions (24) is amply demonstrated by the many conflicting data seen in the literature regarding the characteristics of spinal anesthesia when using plain bupivacaine 0.5%. Despite apparent similarities in methodology, differences in times to onset, maximum levels of sensory blockade achieved, and regression of anesthesia exist, indicating that apart from the variability caused by different investigators, there must be unknown factors that exert a considerable influence. In our study, the average time to onset of maximum cephalad spread was more than 20 min in both groups; although this finding contrasts with some studies reporting shorter onset times (16,25,26), it agrees with others (27). The maximum level of sensory blockade was significantly higher in patients given the bupivacaine solution previously equilibrated to 37°C; also, variability of this higher maximum level was significantly less than in patients receiving the 20°C solution as illustrated by the smaller SEM. These results are consistent with those of a previous study (22). Compared with cerebrospinal fluid of 37°C, the plain solution of bupivacaine 0.5% is isobaric at 20°C and slightly hypobaric at 37°C; this explains the higher maximum level of sensory blockade in patients in group 1.

As might be expected with a higher maximum level of sensory blockade, time to two-segment regression of the sensory level was shorter in group 1 than in group 2, although the difference did not reach statistical significance. The time for regression of the sensory level to the first lumbar segment was also not significantly different; since the maximum level of sensory blockade was higher in group 1, regression to the first lumbar segment obviously involved more segments, indicating that the average time for regression per segment is shorter in group 1. As can be seen from Figure 1, the average levels of sensory blockade were significantly higher in group 1 at all times. Two more practical ways of assessing the differences in regression are 1) the duration, defined as the average time that the sensory level of blockade is at or above a certain thoracic segment, or 2) the number of patients with a sensory level at or above T 10 as a function of time. The former is shown in Figure 2, the latter in Figure 3. As shown in Figure 2, the sensory level of blockade remains significantly longer at or above T 6, T 8, and T 10 in patients in group 1 than in patients in group 2. This means that the shorter average time for regression per segment notwithstanding, the previous equilibrating of the bupivacaine solution to 37°C as compared with the use of a solution at room temperature results not only in a higher, more predictable level of sensory analgesia, but also provides a sensory block with a longer duration.

As can be seen from Figure 3, in five patients in group 2 the sensory level of analgesia remained below T 10, whereas in group 1 the level of sensory blockade was above T 10 in all patients.

Two of the patients in group 1 needed analgetic supplementation while the level of sensory blockade at the time was T 7; one patient experienced pain during manipulation of the peritoneum in the inguinal region, the other during traction on the spermatic cord. This indicates that in these two patients the intensity of sensory blockade was insufficient for visceral stimulation; this phenomenon has been observed in another study, in which a patient experienced pain on bladder distention while the sensory level of blockade was T 6 (26). It is conceivable that the intensity of sensory blockade varies inversely with the number of dermatomes blocked, especially where the higher thoracic dermatomes are concerned, and that when using a plain bupivacaine solution previously equilibrated to 37°C with the intention of achieving a high level of sensory blockade, a higher dose of bupivacaine may be necessary in order to secure adequate analgesia for all patients.

When 15 mg or more of the plain solution of bupivacaine 0.5% is administered with the patient in a sitting position, motor blockade of the lower limbs is reported to be 80 to 100% complete (16–22,25–29). In our study, motor blockade of the lower limbs was complete in all patients and duration of complete motor blockade was similar in both groups.

The decreases in systolic blood pressures in relation to baseline levels were more pronounced in group 1, which is consistent with the higher maximum level of sensory blockade in this group. Ephedrine, which was given when physical signs of low blood pressure were apparent or when systolic blood pressure fell below 90 mm Hg, was administered to five patients in group 1 and to one patient in group 2.

Under the conditions of the present study the use of a solution of plain bupivacaine 0.5% previously equilibrated to 37°C as compared with a solution of 20°C results in a significantly higher, more predictable level of sensory blockade. Onset of sensory and motor blockade, the time needed for regression of two segments and for regression to the first lumbar segment as well as for regression of complete motor blockade to class 2 on the scale of Bromage were similar. Average durations of sensory blockade at or above T 6, T 8, and T 10 were significantly longer in patients receiving the solution of 37°C.

References

1. Nolte H, Schikor K, Gergs P, Meyer J, Stark P. Zur Frage der Spinalanaesthesie mit isobarem Bupivacain 0.5%. Anaesthesist 1977;26:33–7.
2. Stratmann D, Gotte A, Meyer-Hamme K, Watermann W. Klinische Verlaufe von über 6000 Spinalanaesthesien mit Bupivacain. Reg Anaesth 1979;2:49–56.

3. Nightingale PJ, Marstrand T. Subarachnoid anaesthesia with bupivacaine for orthopaedic procedures in the elderly. Br J Anaesth 1981;53:369–71.
4. Tattersall MP. Isobaric bupivacaine and hyperbaric amethocaine for spinal analgesia. A clinical comparison. Anaesthesia 1983;38:115–9.
5. Bion JF. Isobaric bupivacaine for spinal anaesthesia in acute war injuries. Anaesthesia 1984;39:554–9.
6. Nolte H, Stark P. Die Dosis—Wirkungsrelation des isobaren Bupivacain zur Spinalanaesthesie. Reg Anaesth 1979;2:1–4.
7. Cameron AE, Arnold RW, Ghoris MW, Jamieson V. Spinal analgesia using bupivacaine 0.5% plain: variation in the extent of the block with patient age. Anaesthesia 1981;36:318–22.
8. Chambers WA, Edström HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. Br J Anaesth 1981;53:279–82.
9. Chambers WA. Editorial. Br J Anaesth 1982;54:799–801.
10. Nightingale PJ. Barbotage and spinal anaesthesia. Anaesthesia 1983;38:7–9.
11. Cummings GC, Bamber DB, Edström HH, Rubin AP. Subarachnoid blockade with bupivacaine. Br J Anaesth 1984; 56:573–9.
12. Møller IW, Fernandes A, Edström HH. Subarachnoid anaesthesia with 0.5% bupivacaine: effect of density. Br J Anaesth 1984;56:1191–4.
13. Phelan DM, MacEvilly M. A comparison of hyper- and isobaric solutions of bupivacaine for subarachnoid block. Anaesth Intensive Care 1984;12:101–7.
14. Pitkänen M, Haapaniemi L, Tuominen M, Rosenberg PH. Influence of age on spinal anaesthesia with isobaric 0.5% bupivacaine. Br J Anaesth 1984;56:279–84.
15. Logan MR, McClure JH, Wildsmith JAW. Plain bupivacaine: an unpredictable spinal anaesthetic agent. Br J Anaesth 1986; 58:292–6.
16. Kalso E, Tuominen M, Rosenberg PH. Effect of posture and some c.s.f. characteristics on spinal anaesthesia with isobaric 0.5% bupivacaine. Br J Anaesth 1982;54:1179–84.
17. Sheskey MC, Rocco AG, Bizzarri-Schmid M, Francis DM, Edström HH, Covino BG. A dose-response study of bupivacaine for spinal anesthesia. Anesth Analg 1983;62:931–5.
18. Axelsson KH, Edström HH, Widman GB. Spinal anaesthesia with glucose-free 0.5% bupivacaine: effects of different volumes. Br J Anaesth 1984;56:271–8.
19. Bengtsson M, Edström HH, Löfström JB. Spinal analgesia with bupivacaine, mepivacaine and tetracaine. Acta Anaesthesiol Scand 1983;27:278–83.
20. Krüger D, Iphie P, Nolte H, Edström HH. Effekt der Glukosekonzentration auf Spinalanaesthesien mit Bupivacain 0.5%. Reg Anaesth 1983;6:1–3.
21. Stienstra R, Van Poorten JF. Plain or hyperbaric bupivacaine for spinal anesthesia. Anesth Analg 1987;66:171–6.
22. Stienstra R, Van Poorten JF. The temperature of bupivacaine 0.5% affects the sensory level of spinal anesthesia. Anesth Analg 1988;67:272–6.
23. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand 1965;16(Suppl):55–69.
24. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. Anesth Analg 1985;64:715–30.
25. Tuominen M, Kalso E, Rosenberg PH. Effects of posture on the spread of spinal anaesthesia with isobaric 0.75% or 0.5% bupivacaine. Br J Anaesth 1982;54:313–8.
26. Alston RP. Spinal anaesthesia with 0.5% bupivacaine 3 mL. Comparison of plain and hyperbaric solutions administered to seated patients. Br J Anaesth 1988;61:385–9.
27. Gielen MJM, De Grood PMRM, Edström HH. Isobaric bupivacaine 0.5% and hyperbaric lidocaine 5% in spinal anesthesia. Reg Anesth 1987;12:122–7.
28. Bengtsson M, Malmqvist L-A, Edström HH. Spinal analgesia with glucose-free bupivacaine—effects of volume and concentration. Acta Anaesthesiol Scand 1984;28:583–6.
29. Mitchell RWD, Bowler GMR, Scott DB, Edström HH. Effects of posture and baricity on spinal anaesthesia with 0.5% bupivacaine 5 mL. Br J Anaesth 1988;61:139–43.

Abdominal Muscle Activity and Intraabdominal Pressure after Upper Abdominal Surgery

John E. Duggan, MBBS, FFARCS and Gordon B. Drummond, MA, FFARCS

DUGGAN JE, DRUMMOND GB. Abdominal muscle activity and intraabdominal pressure after upper abdominal surgery. Anesth Analg 1989;69:598–603.

To examine the influence of abdominal muscle activity on intraabdominal pressure, the integrated surface EMG from upper abdominal muscle (E_{AB}) was related to changes in intragastric pressure (P_{GA}) in six patients after upper abdominal surgery. A similar respiratory pattern of EMG activity was observed in all subjects. E_{AB} increased rapidly at the onset of expiration, and thereafter more slowly throughout expiration. At the onset of inspiration E_{AB} decreased abruptly, and was small during inspiration. Changes in intragastric pressures were closely related to changes in E_{AB}. In five patients P_{GA} and E_{AB} waveforms were almost identical over the respiratory cycle. In one subject a biphasic change in P_{GA} during inspiration was observed, suggesting the influence of other respiratory muscles. Abdominal muscle action results in changes in intraabdominal pressure previously attributed to diaphragmatic impairment.

Key Words: MEASUREMENT TECHNIQUES, ELECTROMYOGRAPHY. MUSCLE, ABDOMINAL—pattern of activity postoperatively. SURGERY, ABDOMINAL.

Patients undergoing upper abdominal surgery frequently develop abnormal respiratory function after operation with reduction in end-expiratory lung volume that has been attributed, in part, to reflex spasm of the abdominal muscles (1). We have shown that after abdominal surgery there is frequently an increase in abdominal muscle activity during expiration in the abdominal and lower intercostal muscles (2). However, the mechanical effect of muscle activity was not directly measured in that study. The present study was designed to assess the effects of changes in abdominal muscle activity on the time-course of intraabdominal pressure during breathing in patients after upper abdominal surgery. This relationship is important because of the suggestion that diaphragmatic activity is impaired by abdominal operation, based on observations of changes in abdominal pressure with breathing (3).

Methods

We studied six otherwise healthy patients, of either sex, who had undergone elective operations for cholecystectomy ($n = 3$) or gastric procedures ($n = 3$). They were free from respiratory disease and had given informed verbal consent for the study. The study was approved by the local ethics advisory committee, which did not require that written consent be obtained.

Anesthesia was standardized. Premedication was with oral temazepam 20 mg 2 hr before surgery. Anesthesia was induced with thiopental 4–7 mg/kg and maintained with enflurane (1–2% inspired concentration) and nitrous oxide (70% inspired concentration) in oxygen. Tracheal intubation was facilitated with succinylcholine, and muscle relaxation was obtained with alcuronium and was antagonized at the end of the procedure with neostigmine. Complete reversal of neuromuscular blockade was confirmed by stimulation of the ulnar nerve. After recovery from anesthesia, morphine was given IV for pain relief (up to 10 mg) with analgesia thereafter maintained with an infusion of morphine sulfate (up to 1 mg/kg over 24 hr, supplemented if necessary with small IM doses.

Three hours after surgery, simultaneous recordings of intragastric pressure (P_{GA}), abdominal muscle EMG activity (E_{AB}), nasal airflow, and the electrocardiogram (ECG) were made over a 10-min period during quiet tidal breathing with the patient in the supine position.

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Table 1. Patient Characteristics and Surgical Details

Sex	Age (years)	Height (cm)	Weight (kg)	Operation	Incision
F	51	163	64	Chole	RUQ transverse
M	64	168	72	Chole	RUQ transverse
M	37	179	67	HSV	Upper midline
M	38	177	65	HSV	Upper midline
F	48	175	82	Chole	RUQ transverse
F	39	177	79	HSV	Upper midline

Chole: cholecystectomy; HSV: highly selective vagotomy; and RUQ: right upper quadrant.

Intragastric pressure was measured using a transducer (Sanborn 207a, Waltham, MA) attached by a sidearm to a nasogastric tube (14 FG) with its tip positioned in the stomach. The tube was first flushed with physiologic sodium chloride solution and then kept patent with a slow constant infusion of sodium chloride solution at 10 mL/hr. Measurement of P_{GA} in this way avoided the introduction of an intragastric balloon in addition to the nasogastric tube already in place. This method gives measurements of intragastric pressure which correlate well with the gastric balloon method (4,5).

Nasal airflow was measured using the method of Guyatt and coworkers (6). Oxygen was administered at 2 L/min by nasal cannulae positioned within the external nares of the patient. These cannulae also acted as nasal pitot tubes. Pressure fluctuations at a sidearm at the upstream end of the supply tube were measured with a differential pressure transducer, which was connected between the sidearm and a balance reference tube that also carried an oxygen flow. The bias flow was adjusted so that when no flow was present at the nose the pressure difference across the transducer was zero. This method was validated as a qualitative index of the phases of respiration by comparison of the flow signal with measurements of rib cage and abdominal motion using impedance bands around the rib cage and abdomen, and it gave an accurate index of the phases of respiration. The nasal flow signal was used to identify three phases of the respiratory cycle: inspiration (I), expiration (E), and an expiratory pause (EP).

Abdominal muscle EMG was measured using two pregelled silver-silver chloride electrodes with 1 cm diameter pads (Medicotest). The skin was prepared with an abrasive jelly and an organic solvent so that the interelectrode resistance was typically less than 2 kΩ. The electrodes were placed with their centers 4 cm apart, 2 cm below the left costal margin, lateral to the mass of the rectus abdominis, so that the activity they picked up was predominantly that of the external oblique muscle. A reference electrode was placed on the iliac crest. The EMG signal was amplified and filtered with a bandwidth of 20 Hz to 2 kHz (Neurolog NL 104/125, Digitimer Ltd., Welwyn Garden City, Herts, UK) and recorded with an FM tape recorder (Digitimer D146) along with the ECG (lead II), P_{GA}, and nasal airflow signals. Zero activity for the EMG signal was recorded at the end of each assessment by placing the electrodes face to face.

The recorded signals were played back onto a UV galvanometer recorder (Bell and Howell 5-137, Basingstoke, Herts, UK). The EMG signal was passed through a delay network, and, using a method similar to that described by Muller and coworkers (7), the contribution of the ECG artifact was gated out. The signal was then full wave rectified and integrated as an exponential time weighted average using a "leaky integrator" (NL 103) with a time constant of 100 mS. The EMG signals were calibrated by passing a known voltage through the same network to the recorder.

In each patient 30 consecutive breaths were analyzed in detail. The relationship between E_{AB} and P_{GA} was assessed by measuring the changes in these values that occurred during inspiration, expiration, and the expiratory pause, and interrelating those changes by means of least squares linear regression analysis (8).

Results

Details of patient characteristics and operations performed are given in Table 1. A representative sample of nasal airflow and P_{GA} and E_{AB} signals in a subject after cholecystectomy is illustrated in Figure 1. The phases of each breath (I, E, and EP) are identified by changes in nasal airflow and separated by the dashed lines A, B, C, and D. The changes in P_{GA} and E_{AB} that occurred over these phases were measured by subtracting the value at the beginning of each phase from the value at the end of that phase: a negative value indicates a decrease in the variable over the respiratory phase under study. For example, the change in P_{GA} that occurred over inspiration in Figure 1 is

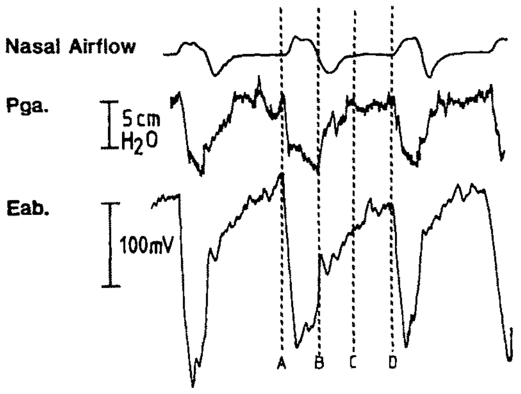

Figure 1. Representative record of nasal airflow, intragastric pressure (P_{GA}), and abdominal muscle activity (E_{AB}) (amplification before integration 10K). The phases of each breath are identified by changes in nasal airflow and separated by the dashed lines. A: onset of inspiratory airflow; B: onset of expiratory airflow; C: end of expiration; and D: onset of next inspiration.

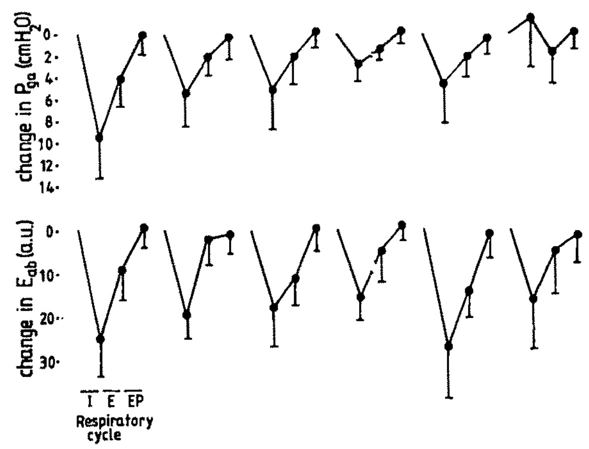

Figure 2. Mean changes (SD) in E_{AB} (a.u.) and in P_{GA} (cm H_2O) observed over the different phases of respiration (I: inspiration; E: expiration; EP: expiratory pause) in 30 consecutive single breaths for each subject.

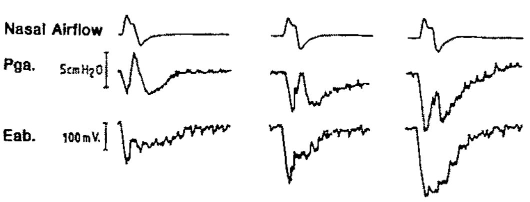

Figure 3. Nasal airflow, intragastric pressure (P_{GA}), and abdominal muscle activity (E_{AB}) (amplification before integration 20K) recorded from subject 6, in whom a biphasic pressure change was observed during inspiration. Three separate breaths are shown that differ in the amount of end-expiratory abdominal muscle activity (increasing from left-hand to right-hand traces). There is a consistent increase in P_{GA} in late inspiration, and P_{GA} is otherwise closely related to changes in E_{AB}.

obtained by subtracting the value of P_{GA} at point A (onset of inspiratory flow) from the value at point B (onset of expiratory flow).

Phasic activity of the abdominal muscles in time with respiration can be seen in the recording of E_{AB} illustrated in Figure 1. This pattern was present throughout the observation period in all six patients studied. The following features were seen consistently: 1) There was little detectable EMG activity during inspiration; 2) E_{AB} increased rapidly with the onset of expiratory airflow; 3) there was a subsequent progressive increase in E_{AB} throughout expiration and the expiratory pause; and 4) E_{AB} decreased abruptly at the onset of inspiratory airflow. In Figure 1, it can be seen clearly that the variations in P_{GA} over a respiratory cycle resemble the variations in E_{AB} over the same cycle. At the onset of inspiratory airflow, P_{GA} shows a rapid decrease, which can be related in time to the change in E_{AB}. P_{GA} continues to decrease throughout most of the duration of inspiration, although at a much slower rate, reaching a nadir in late inspiration. An increase in P_{GA} was noted commonly just before the onset of expiratory airflow, followed by a progressive increase in pressure throughout expiration and the expiratory pause. The mean changes in P_{GA} and E_{AB} over 30 consecutive single breaths for the different phases of respiration in each subject are shown in Figure 2. For subjects 1 through 5, the similarity in the waveform of P_{GA} and E_{AB} in individual subjects is indicated by the common pattern of the mean changes in P_{GA} and E_{AB}. However, in patient 6 this relationship is not evident, despite a similar phasic pattern of abdominal muscle activity.

Subject 6 showed a more complex P_{GA} waveform, with a biphasic pressure change during inspiration (Figure 3). As in the other five subjects, P_{GA} decreased at the start of inspiration and was related in magnitude to the decrease in E_{AB}. However, this initial decrease in P_{GA} was consistently followed by a positive pressure wave, beginning in late inspiration and becoming maximal at the end of inspiratory airflow. The three breaths illustrated in Figure 3 were chosen to show different degrees of end-expiratory muscle activity, less in the left-hand and more in the right-hand tracings. In each of these three breaths, at the onset of inspiration, the magnitude of the initial decrease in P_{GA} can be related to the magnitude of change in E_{AB}, which is progressively greater from left-hand to right-hand tracings. The positive pressure wave can be seen clearly in late inspiration in each breath, with a similar amplitude and time-course. Thus, in the three sample breaths shown, the overall change in P_{GA} during inspiration consists of the initial decrease and the late positive wave. When the initial decreasing component of P_{GA} is small, as in

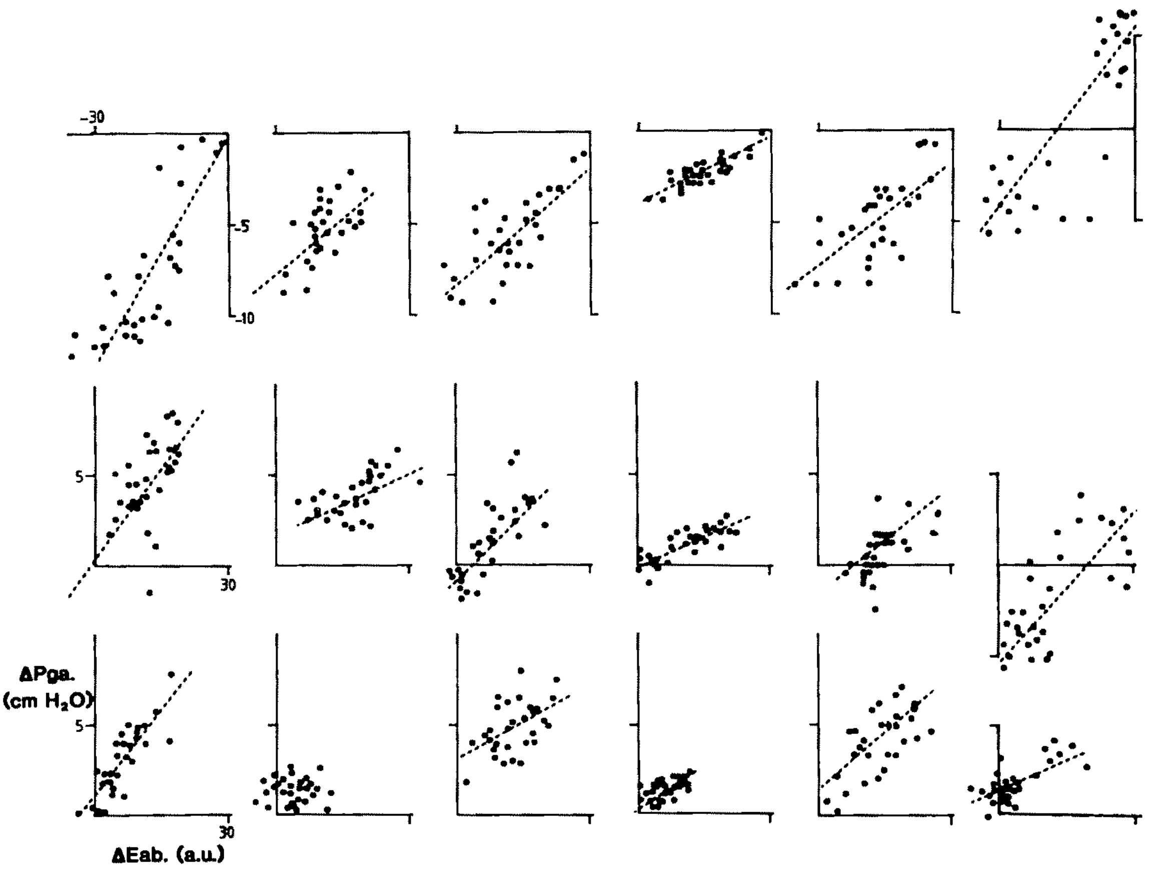

Figure 4. Plots of changes in P_{GA} (cm H_2O) and E_{AB} (a.u.) ove each phase of respiration for 30 consecutive single breaths. Eac column represents another patient, from patient 1 (on the lef through patient 6 (on the right). Top row: inspiration; middle ro expiration; and bottom row: expiratory pause. The regression lin are shown. Regression details are given in Table 2.

the first breath, the overall change in P_{GA} during inspiration is positive. In breaths 2 and 3, as the initial decreasing component of P_{GA} becomes greater, the overall change in P_{GA} over inspiration at first decreases within the positive range (breath 2), and then becomes negative (breath 3).

Examination of recordings, and mean values calculated from all the breaths analyzed, of the changes in P_{GA} and E_{AB} during each part of the respiratory cycle indicated that between patients, the degree of change in P_{GA} was related to changes in E_{AB}. However, each patient had considerable breath-to-breath variation in the changes noted for each of these variables. Consequently, the use of mean values obtained from each patient over a number of breaths obscures the exact relationship of P_{GA} and E_{AB}. To examine this relationship further, and to assess the relative contribution of the pattern of abdominal muscle activation to changes in intragastric pressure, we plotted for each patient the changes in E_{AB} and P_{GA} observed in each phase of the respiratory cycle for 30 consecutive breaths (Figure 4). The slopes of the regression lines of the E_{AB} and P_{GA} plot for each phase of respiration, and the coefficients of linear regression of these relationships, are given in Table 2.

In each patient there was a close relationship betwee the changes in E_{AB} and P_{GA} during I, E, and EP. Th slopes of the regression lines obtained in each phas of respiration were similar in individual patients. I patients 1 through 5, the intercepts of the regressio lines are close to the origin of the plot of E_{AB} and P_{GA} In addition, some observed points fall close to th origin of the plot, suggesting that when the activity c the abdominal muscles did not change during th respiratory cycle, the change in intraabdominal pres sure associated with respiration was small. Althoug a similar correlation between changes in E_{AB} and P_{G} was present in patient 6, Figure 4 shows that in thi patient the relationships of E_{AB} and P_{GA} did not pas close to the intercept of the plot. For inspirator changes, the regression line was shifted to the lef and for the expiratory changes the line was shifted a equivalent amount to the right, although the slope of the regression lines remain similar.

Table 2. Regression Relationships for Changes in P_{GA} and E_{AB} for Each Patient in Each Phase of Respiration

	Linear regression coefficient			Slope of regression line (cm H_2O/a.u.)		
Subject	I	E	EP	I	E	EP
1	0.84	0.57	0.82	0.43	0.35	0.32
2	0.59	0.56	0.25	0.17	0.11	0.05
3	0.72	0.63	0.46	0.19	0.21	0.13
4	0.84	0.80	0.4	0.12	0.11	0.16
5	0.73	0.6	0.68	0.17	0.16	0.17
6	0.78	0.56	0.62	0.37	0.37	0.10

I: inspiration; E: expiration; and EP: expiratory pause.

Discussion

In this study we consistently observed expiratory activity of the muscles of the upper abdominal wall. This confirms the findings in a previous study (2) in which 18 similar patients showed the same pattern of muscle activity, in the lower intercostal, upper abdominal, and lower abdominal muscles. This suggests that the muscles surrounding the abdominal contents usually have phasic respiratory activity after upper abdominal surgery.

It is clear from the similar time-course of the changes in P_{GA} and E_{AB} during breathing, and the individual linear correlations between the breath-to-breath changes in these two variables (Figure 4), that this phasic pattern of abdominal muscle activity directly affects intraabdominal pressure. The magnitude of the changes of P_{GA} associated with the variations in EMG activity suggests that this pattern of abdominal muscle action has a significant influence on the mechanics of breathing. Expiratory activity of the abdominal muscles has also been reported in dogs up to 1 hr after cholecystectomy (9). In normal humans, expiratory activity of the abdominal muscles is only found when minute ventilation is great (10–12).

However, the abdominal muscles become active in humans during expiration when breathing is unstimulated in the lightly anesthetized state (13). In that study, performed in volunteers without surgical stimulation, the pattern of P_{GA} change was remarkably similar to that observed in the present study after upper abdominal surgery. The present study was performed 3 hr after recovery from anesthesia and conducted with agents associated with rapid recovery, so that residual effects of the anesthetic agents are unlikely to have been responsible for the findings of this study.

Breathing influences intraabdominal pressure by the action of inspiratory muscles, both those of the rib cage and those of the diaphragm. Inspiratory activity of these two muscle groups has opposite effects on intraabdominal pressure: diaphragmatic contraction increases intraabdominal pressure, whereas inspiratory action of the muscles of the rib cage reduces intraabdominal pressure. In normal subjects in the supine posture inspiration is predominantly a result of diaphragmatic activity, and intraabdominal pressure increases during inspiration (14). In subjects 1 through 5, because intraabdominal pressure changed little during inspirations when there was little change in abdominal muscle activity, both the rib cage muscles and diaphragm must have been active during inspiration, and acting in a way to minimize the transmission of the decrease in pleural pressure to the abdominal cavity. In the sixth subject, intraabdominal pressure increased in late inspiration, and there was evidence on the E_{AB}/P_{GA} plot of an independent factor that influenced P_{GA}; this suggests that muscles exerting a positive influence on P_{GA} were active at the end of inspiration, which is consistent with either a greater action of the diaphragm or relatively less action of rib cage muscles during inspiration in this subject compared to the others.

Activity of the abdominal muscles can reduce lung volume, both directly, because of their insertion at the lower rib cage, and indirectly, by displacing the relaxed diaphragm cranially secondary to increases in intraabdominal pressure. The abrupt offset of abdominal muscle activity can thus contribute to inspiration, if expiratory activity of the abdominal muscles has reduced the volume of the respiratory system to less than the passive functional residual capacity. This is observed in patients with bilateral phrenic nerve palsy (15).

A sudden reduction of abdominal muscle activity at the onset of inspiration may impair the action of the diaphragm. Contraction of the diaphragm is normally accompanied by elevation of the lower rib cage, and this effect is dependent on the "fulcrum effect" of the abdominal contents (16), whereby the increase in intraabdominal pressure caused by the tense diaphragm also generates a lateral force on the lower rib cage. Thus a reduction in intraabdominal pressure associated with the offset of abdominal muscle activity, when diaphragmatic activity is increasing, may result in a less efficient mechanical coupling of diaphragmatic contraction to lower rib cage movement.

It is evident that expiratory abdominal muscle recruitment has to be considered in the analysis of respiratory impairment after abdominal surgery. Several methods of analysis have been advanced. Two are based on the relative pressure changes in abdominal and pleural compartments: the "diaphragmatic index" used by Gilbert, Auchincloss, and Peppi (17), which is the ratio between changes in intraabdominal pressure during inspiration and the change in transdiaphragmatic pressure over the same period ($\Delta P_{AB}/\Delta P_{DI}$), and the index used by Ford and colleagues (3) of the ratio between the change in abdominal pressure and the change in pleural pressure during inspiration ($\Delta P_{AB}/\Delta P_{PL}$). A further index is based on the analysis by Konno and Mead of the motion of the rib cage and abdomen during breathing (18), and is expressed as the relative change in dimensions of the rib cage (RC) and abdomen (AB) [$\Delta AB/(\Delta AB+\Delta RC)$]. After abdominal surgery, changes in both the pressure indices (3,19,20) and the motion index (3,21) have been interpreted as showing a marked degree of diaphragmatic impairment. Epidural analgesia with bupivacaine causes these indices to change toward the preoperative values (22).

The above indices of pressure and motion attempt to assess the relative action of the diaphragm and rib cage muscles in a system in which the abdominal muscles may also contribute to both pressure and movement. If the abdominal muscles have phasic respiratory activity, such as after abdominal surgery, these indices are unlikely to be of value. For example, a reduction in abdominal muscle activity on inspiration will yield pressure indices suggesting greater rib cage activity, because these muscles have an opposite action on intraabdominal pressure. We conclude that phasic respiratory activity of the abdominal muscles is common after abdominal surgery. Abdominal muscle action should be considered in the analysis of respiratory movement and pleural and abdominal pressure changes after abdominal surgery. Previous conclusions concerning postoperative diaphragmatic activity need to be reevaluated in light of these findings.

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References

1. Craig DB. Postoperative recovery of pulmonary function. Anesth Analg 1981;60:46–52.
2. Duggan J, Drummond GB. Activity of lower intercostal an abdominal muscle after upper abdominal surgery. Anest Analg 1987;66:852–5.
3. Ford GT, Whitelaw WA, Rosenal TW, Cruse PJ, Guenter C Diaphragm function after upper abdominal surgery in h mans. Am Rev Respir Dis 1983;127:431–6.
4. Drummond GB, Park GR. Changes in intragastric pressure o induction of anaesthesia. Br J Anaesth 1984;56:873–9.
5. Le Souef PN, Lopes JM, England SJ, Bryan MH, Bryan A Effects of chest wall distortion on occlusion pressure and t preterm diaphragm. J Appl Physiol: Respirat Environ Exercis Physiol 1983;55:359–64.
6. Guyatt AR, Parker SP, McBride MJ. Measurement of huma nasal ventilation using an oxygen cannula as a pitot tube. A Rev Respir Dis 1982;126:434–8.
7. Muller N, Volgyesi G, Becker L, Bryan MH, Bryan A Diaphragmatic muscle tone. J Appl Physiol: Respirat Enviro Exercise Physiol 1979;47:279–84.
8. Freund JE. Modern Elementary Statistics, 3d ed. Englewoo Cliffs, N.J.: Prentice-Hall, 1967:331.
9. Dureuil B, Viires N, Marty C, Aubier M, Pariente R, Desmon J-M. Effects of cholecystectomy on phrenic output and resp ratory muscles function (abstract). Anesthesiology 198 63:A517.
10. Campbell EJM, Green JH. The behaviour of the abdomin muscles and the intra-abdominal pressure during quiet breat ing and increased pulmonary ventilation. A study in man. Physiol (Lond) 1955;127:423–6.
11. Hill AR, Kaiser DL, Rochester DF. Effects of thoracic volu and shape on electromechanical coupling in abdominal mu cles. J Appl Physiol: Respirat Environ Exercise Physiol 198 56:1294–301.
12. Oliven A, Deal EC Jr, Kelsen SG, Cherniack NS. Effects hypercapnia on inspiratory and expiratory muscle activit during expiration. J Appl Physiol: Respirat Environ Exercis Physiol 1985;59:1560–5.
13. Freund F, Roos A, Dodd RB. Expiratory activity of the abdon inal muscles in man during general anesthesia. J Appl Physi 1964;19:693–7.
14. Agostoni E. Statics. In Cambell EJM, Agostoni E, Newso Davis J, eds. The Respiratory Muscles: Mechanics and Neur Control, 2d ed. London: Lloyd-Luke, 1970:48–79.
15. Loh L, Goldman M, Newsom Davis J. The assessment diaphragm function. Medicine 1977;56:165–9.
16. Goldman MD, Mead J. Mechanical interaction between t diaphragm and rib cage. J Appl Physiol 1973;35:197–204.
17. Gilbert R, Auchincloss JH, Peppi D. Relationship of the r cage and abdomen motion to diaphragm function during qui breathing. Chest 1981;80:607–12.
18. Konno K, Mead J. Measurement of the separate volu changes of rib cage and abdomen during breathing. J Ap Physiol 1967;22:407–21.
19. Dureuil B, Viires N, Cantineau J-P, Aubier M, Desmonts J- Diaphragmatic contractility after upper abdominal surgery. Appl Physiol: Respirat Environ Exercise Physiol 1986;61:177 80.
20. Simonneau G, Vivien A, Sartene R, et al. Diaphragm dysfun tion induced by upper abdominal surgery. Am Rev Respir D 1983;128:899–903.
21. Dureuil B, Cantineau J-P, Desmonts J-M. Effects of upper lower abdominal surgery on diaphragmatic function. Br Anaesth 1987;59:1230–5.
22. Mankikian B, Cantineau JP, Bertrand M, Kieffer E, Sartene Viars P. Improvement of diaphragmatic function by a thorac extradural block after upper abdominal surgery. Anesthesi ogy 1988;68:379–86.

Transient Maternal Hypotension following Epidural Anesthesia

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PHILIPSON EH, KUHNERT BR, PIMENTEL R, AMINI SB. Transient maternal hypotension following epidural anesthesia. Anesth Analg 1989;69:604–7.

Transient maternal hypotension following regional anesthesia can lead to significantly lower umbilical cord pH values. Although this acidosis has not been found to be clinically significant, acidosis may increase the placental transfer of local anesthetic agents as a result of "ion trapping." The purpose of this study was to examine the pharmacologic and clinical consequences of transient maternal hypotension following epidural anesthesia. Forty women at term received an epidural anesthesia with 0.5% bupivacaine before cesarean section. Patients were divided into two groups based on the development of maternal hypotension, defined as a systolic blood pressure less than 100 torr or a decrease of 30% or more from the preanesthetic level. Thirteen patients (33%) developed hypotension that was corrected within 2 1 ± 1.8 min. The pH of umbilical cord venous and arterial blood and the concentration of bupivacaine were significantly lower ($P <$ 0.05) in neonates of mothers in the hypotensive group than in neonates of mothers that did not develop hypotension. The results show, however, that transient maternal hypotension following epidural anesthesia does not lead to a greater placental transfer of bupivacaine due to "ion trapping" even though neonatal cord blood pH decreases.

Key Words: ANESTHESIA, OBSTETRIC—hypotension. ANESTHETIC TECHNIQUES, EPIDURAL—obstetric.

Maternal hypotension is one of the most common complications of obstetrical lumbar epidural anesthesia (1,2). Hypotension may lead to utero-placental hypoperfusion and fetal acidosis (3). However, when the hypotension is rapidly corrected and hence transient, even though significantly lower umbilical cord vein and artery pH values have been reported, these are without any clinical consequences to the neonate (4).

Fetal acidosis can influence the disposition of local anesthetic agents. Acidosis may cause the ionized form of the local anesthetic to become "trapped" on the fetal side of the placenta and increase its net transfer across the placenta (5). An increase in placental transfer of bupivacaine following epidural anesthesia has been shown in acidotic infants (6). With transient maternal hypotension and changes in pH, the potential for "ion trapping" and an increase in placental transfer of local anesthetic agents exists. The purpose of this study was 1) to examine the pharmacologic consequences of transient maternal hypotension following epidural anesthesia with bupivacaine for cesarean section, and 2) to verify previous clinical results of this complication.

Materials and Methods

Patients

All patients had normal singleton term gestations. These patients were scheduled for elective cesarean section in the morning at Cleveland Metropolitan General Hospital and were not in labor. None of the patients had a history of liver or kidney disease or known drug abuse. This prospective study was approved by the hospital human investigation committee, and appropriate informed consent was obtained prior to the study.

Procedure

Prior to the procedure, all patients received a rapid intravenous infusion of at least 1 L of normal saline or

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Ringer's lactate solution. An anesthesiologist administered the epidural anesthesia using 0.5% bupivacaine without epinephrine. All patients were placed on the operating room table in the supine position with left lateral uterine displacement and were given oxygen at 4 L/min by nasal cannula before the bupivacaine was injected. Following a test dose (3 mL), bupivacaine in incremental doses of 5 mL was given to obtain a sensory block to T_3–T_4 dermatome. Maternal blood pressure was measured every minute with an Arteriosonde (Kontron Inc., Everett, MA) from the time of epidural anesthesia until delivery of the infant and every 5 min until completion of surgery. Maternal hypotension was identified when the systolic blood pressure was less than 100 torr or when there was a decrease of 30% or more from the preanesthetic baseline level. Ephedrine was not used prophylactically. If hypotension developed, it was immediately corrected by incremental doses of intravenous ephedrine (5–10 mg) and by increasing the rate of infusion of the intravenous solution. The total doses of bupivacaine and ephedrine as well as both times from bupivacaine administration to delivery (drug–delivery interval) and from the initial recording of hypotension to a normotensive blood pressure (recovery time) were recorded.

Sample Collection

Maternal blood samples (3 mL) from a peripheral arm vein were obtained at delivery coincident with clamping of the umbilical cord. Neonatal blood samples were obtained at birth from a doubly clamped section of cord. All samples were drawn into heparin anticoagulant tubes and immediately placed on ice. The plasma was removed following centrifugation and frozen until assayed for drug levels.

Clinical Outcome

The neonatal clinical effects were monitored by the 1- and 5-min Apgar scores and acid–base status of the umbilical cord at delivery. Blood gas tensions and pH in umbilical cord venous and arterial blood were immediately measured with an automatic gas system (Corning-175). Each infant was weighed and a complete physical examination was performed. The gestational age was determined by the Ballard modification of the Dubowitz examination (7).

Sample Analysis

Plasma samples (3 mL) from the maternal vein and umbilical cord vessels at delivery were analyzed for bupivacaine and its metabolite 2,6-pipecolylxylidine (PPX) by gas chromatography-mass spectometry techniques as previously described (8). The sensitivity of this method is 4 ng/mL.

Data Analysis

Patients were divided into two groups based on the development of maternal hypotension following lumbar epidural anesthesia. The two groups, i.e., normotensive and hypotensive, were characterized by descriptive statistics and the means of outcome variables were compared using two sample *t*-test and Mann–Whitney rank-sum test. Pearson correlation, canonical correlation, and linear regression analysis were used to document simple or multiple correlations between the drug–delivery interval, recovery time, and the bupivacaine concentration in the maternal and umbilical cord vein. A P value of <0.05 was considered statistically significant.

Results

Clinical Effects

Thirteen of the 40 patients (33%) in the study developed hypotension, whereas 27 patients remained normotensive. There were no differences in maternal characteristics between the groups (Table 1). All neonates in the normotensive group were at term and had 1- and 5-min Apgar scores greater than 7. One neonate in the hypotensive group had a 1-min Apgar score of 6. The 5-min Apgar score in this neonate was 8. There were no differences between the groups in the total dose of bupivacaine administered, drug–delivery interval, or uterine incision–delivery interval. The mean dose of ephedrine was 17 ± 8 mg, and the recovery time was 2.1 ± 1.8 min (Table 1).

The effect of maternal hypotension on the umbilical cord vein and artery acid–base status is shown in Table 2. The mean pH was significantly less in the umbilical cord vein ($t = 2.45$, $P < 0.05$) and artery ($t = 2.02$, $P < 0.05$) in hypotensive than in normotensive mothers. There were no significant differences in Pco_2 or Po_2 between the groups.

Pharmacologic Effects

The maternal and umbilical cord plasma concentrations of bupivacaine and its metabolite, PPX, are shown in Table 3. There was no significant difference

Table 1. Maternal, Neonatal, and Intrapartum Characteristics of the Two Study Groups

	Normotensive group (n = 27)	Hypotensive group, (n = 13)
Mothers		
Age (years)	28 ± 6*	25 ± 4
Height (cm)	159 ± 6	162 ± 6
Weight (kg)	75 ± 15	81 ± 18
Hematocrit (%)	35 ± 3	35 ± 4
Neonates'		
Gestational age (weeks)	39 ± 1	39 ± 1
Birthweight (g)	3263 ± 423	3443 ± 555
Apgar score <7		
1-min	0	1
5-min	0	0
Intrapartum anesthesia		
Total dose bupivacaine (mg)	127 ± 27	129 ± 31
Drug–delivery interval (min)	38 ± 8	45 ± 13
Uterine incision–delivery interval (sec)	106 ± 63	143 ± 53
Total dose of ephedrine (mg)	—	17 ± 8
Recovery time (min)	—	2.1 ± 1.8

*Mean ± standard deviation.

Table 2. Effect of Maternal Hypotension on Umbilical Cord Acid–Base Status at Delivery

Umbilical cord	Normotensive group	Hypotensive group	Significance (P value)
Vein			
pH	7.34 ± 0.05*	7.30 ± 0.05	<0.05
Pco$_2$	40.9 ± 4.9	39.9 ± 6.0	NS
Po$_2$	32.1 ± 10.7	29.5 ± 5.2	NS
Artery			
pH	7.26 ± 0.06	7.22 ± 0.08	<0.05
Pco$_2$	52.2 ± 6.7	55.2 ± 8.1	NS
Po$_2$	15.9 ± 5.0	16.1 ± 3.8	NS

NS = not significant.
*Mean ± standard deviation.

between the groups in the bupivacaine concentration in the maternal vein at delivery. The concentration of bupivacaine in the umbilical cord vein was, however, significantly lower in neonates of hypotensive mothers than in normotensive mothers ($t = 2.03$, $P < 0.05$). There was no significant difference in the concentrations of PPX or fetal/maternal ratios between the groups. Although not statistically significant, the fetal/maternal ratio of bupivacaine levels was lower in the hypotensive group than in the normotensive group.

Using the Pearson correlation, there was no significant correlation between umbilical cord bupivacaine concentration and maternal bupivacaine concentration ($r = 0.12$, $P > 0.7$), drug–delivery interval ($r = 0.2$, $P > 0.5$), or recovery time ($r = 0.1$, $P > 0.7$). Further canonical correlation failed to show any significant correlation between the bupivacaine concentrations and time intervals. The first canonical correlation was 0.42, $P = 0.8$.

Table 3. Bupivacaine (ng/mL) and PPX (mg/mL) Concentrations at Delivery in Maternal Plasma and Umbilical Cord in the Two Study Groups

	Normotensive group (n = 27)	Hypotensive group (n = 13)	Significance (P value)
Bupivacaine (ng/mL)			
Maternal vein	1.03 ± 0.52*	1.24 ± 0.73	NS
Cord vein	0.31 ± 0.10	0.21 ± 0.07	<0.05
F/M ratio†	0.37 ± 0.33	0.21 ± 0.12	NS
PPX (mg/mL)			
Maternal vein	0.04 ± 0.05	0.04 ± 0.03	NS
Cord vein	0.04 ± 0.03	0.03 ± 0.01	NS
F/M ratio	0.90 ± 0.54	0.86 ± 0.44	NS

NS = not significant.
*Mean ± standard deviation.
†Level in cord vein/level in maternal vein at delivery. Mean of individual ratios, not ratio of means.

Discussion

The purpose of this study was to examine the clinical and pharmacologic consequences of transient maternal hypotension following lumbar epidural anesthesia with bupivacaine for cesarean section. The results demonstrate that transient maternal hypotension does not lead to a greater placental transfer of bupivacaine due to "ion trapping."

The key finding of this study was the lower concentration of bupivacaine in the umbilical cord vein in the hypotensive group. This lower drug concentration was accompanied by a lower fetal pH and a lower, but not statistically significant, decrease in the fetal/maternal ratio. With this mildly acidotic change, an increased concentration of bupivacaine would have been anticipated if "ion trapping" of bupivacaine occurred. A possible explanation for the lower drug concentration may be due to small differences (although not statistically significant ones) in the drug–delivery or uterine incision–delivery intervals or possibly from decreased transfer across the placenta by a relative utero-placental hypoperfusion in the hypotension group.

Another result of this study is the 33% incidence of maternal hypotension. This incidence is similar to those reported by Brizgys et al. in nonlaboring mothers (36%) and in another study (28%) of women undergoing elective cesarean section (4,9). This high percentage of hypotension may result from insufficient hydration or possibly from the study design when the blood pressure is monitored automatically and frequently. In addition, the maternal hypotension was described as transient, as the mean duration of hypotension in our study was 2.1 min and no adverse neonatal effects were found. Corke et al. also found that a short period of hypotension after spinal analgesia for cesarean section, defined as less than 2 min, was not harmful to the neonates (10). Although Brizgys et al. did not report the duration of the hypotension, maternal hypotension was rapidly corrected and classified as "transient" and without adverse clinical effects (4). Thus, the definition of "transient" hypotension is important because in such cases lower umbilical-cord vein pH values are without adverse clinical consequences. One might expect that a more severe or prolonged hypotensive episode with fetal hypoxia and acidosis may have different clinical and pharmacologic results. However, maternal hypotension, when transient in our study, does not have adverse clinical or pharmacologic consequences.

In summary, despite specific prophylactic measures, maternal hypotension occurs frequently in nonlaboring mothers who receive lumbar epidural anesthesia for cesarean section. Maternal blood pressure should be monitored frequently, so that hypotension is recognized and rapidly treated. Short-lived, rapidly corrected, and hence transient maternal hypotension is not associated with adverse clinical or pharmacologic effects on the neonate.

References

1. Shnider SM, Levinson G. Anesthesia for Obstetrics. Baltimore: Williams and Wilkins, 1987:293.
2. Obstetric Anesthesia and Analgesia. ACOG Technical Bulletin Number 112. January 1988.
3. Marx GF, Cosmi EV, Wollman SB. Biochemical status and clinical condition of mother and infant at cesarean section. Anesth Analg 1969;48:986–94.
4. Brizgys RV, Dailey PA, Shnider SM, et al. The incidence and neonatal effects of maternal hypotension during epidural anesthesia for cesarean section. Anesthesiology 1987;67:782–6.
5. Ralston DH, Shnider SM. The fetal and neonatal effects of regional anesthesia in obstetrics. Anesthesiology 1978;48:34–64.
6. Datta S, Brown WU, Ostheimer GW, et al. Epidural anesthesia for cesarean section in diabetic parturients: Maternal and neonatal acid–base status and bupivacaine concentration. Anesth Analg 1981;60:574–8.
7. Ballard JL, Novak K, Driver M. A simplified score for assessment of fetal maturation and newly born infant. J Pediatr 1979; 95:769–74.
8. Kuhnert PM, Kuhnert BR, Stitts JM, Gross TL. The use of a selected ion-monitoring technique to study the disposition of bupivacaine in mother, fetus, and neonate following epidural anesthesia for cesarean section. Anesthesiology 1981;55:611–7.
9. Philipson EH, Kalhan SC, Riha MM, Pimentel R. Effects of maternal glucose infusion on fetal acid–base status in human pregnancy. Am J Obstet Gynecol 1987;157:866–73.
10. Corke BC, Datta S, Ostheimer GW, et al. Spinal anaesthesia for ceasarean section—the influence of hypotension on neonatal outcome. Anaesthesia 1982;37:658–62.

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Bronchial Cuff Pressures of Double-Lumen Tubes

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Pressure damage to respiratory mucosa from overinflation of bronchial cuffs has been implicated as a cause of bronchial rupture, a rare but devastating complication of double-lumen endobronchial tubes (DLTs). We compared the pressure/volume characteristics of the bronchial cuffs of three different polyvinylchloride (PVC) DLTs and a equivalent sized red-rubber Robertshaw DLT. At the volume needed to seal effectively our bronchial model, two of the three PVC tube cuffs tested generated significantly less pressure than did that of the cuffs of the third PVC and the red-rubber Robertshaw tubes.

Key Words: ANESTHETIC TECHNIQUES, ENDOBRONCHIAL—cuff pressures. EQUIPMENT, TUBES—endobronchial.

Airway trauma from double-lumen endobronchial tubes (DLTs) may result from overinflation of the bronchial cuff, which can lead to ischemic pressure damage to the respiratory mucosa. The association between high intracuff pressure and ischemic injury to the tracheal wall has been previously documented for endotracheal tubes (1), but there have been few reports of bronchial cuff pressure/volume measurements for DLTs. Therefore, we measured the bronchial cuff pressure/volume characteristics of commercially available DLTs to determine whether there were differences between tubes currently in use.

Methods

The 41F polyvinylchloride (PVC) left-DLTs used in this study were provided to us by their manufacturers (Mallinckrodt [Broncho-Cath], Sheridan [Bronco-Trach], Rusch [Bronchial Double-Lumen Tube]). Equivalent sized (large) red-rubber Robertshaw tubes (Leyland) were also used for comparison. Two different tubes of each type were studied with a minimum of three trials for each individual DLT.

Each tube was placed horizontally in a rigid glass cylinder whose diameter (12 mm) equaled the diameter of the average male's left main-bronchus (2). The valve of the pilot balloon was connected to a pressure transducer through saline solution filled tubing. A second transducer was attached to the breathing circuit adaptor of the bronchial lumen. Pressures were transduced and recorded with use of a Marquette 700 RA monitor with a Marquette DDW digital chart recorder at a paper speed of 10 mm/sec. A scale of 0–200 mm Hg was used for the cuff pressure and 0–30 mm Hg for the bronchial lumen pressure. Transducers were set at zero before each determination and were placed at the level of the DLT.

The bronchial lumen of each tube was connected to the breathing circuit of an anesthesia machine (Ohio Modulus) that delivered 10 L/min oxygen. The bronchial cuff was progressively distended by continuous inflation of air with use of a syringe pump (Edco Scientific Model 843). Activation of the pump was simultaneous with a mark on the chart paper with use of a third pressure channel. When the bronchial cuff occluded the inside of the glass cylinder, the pressure within the bronchial lumen began to rise. Occlusion time (and therefore volume) was determined from the chart paper as the first clearly detectable rise of this pressure tracing by an observer, without regard to the tube type. The volume of the air delivered to the cuff was determined from the recorded time with use of the previously calibrated constant delivery rate of the pump. Cuff pressures to 5 mL of cuff volume at 1-mL intervals and occlusion time were recorded.

Data are presented as the mean ± SD. The hypothesis that there was a difference between tube types in

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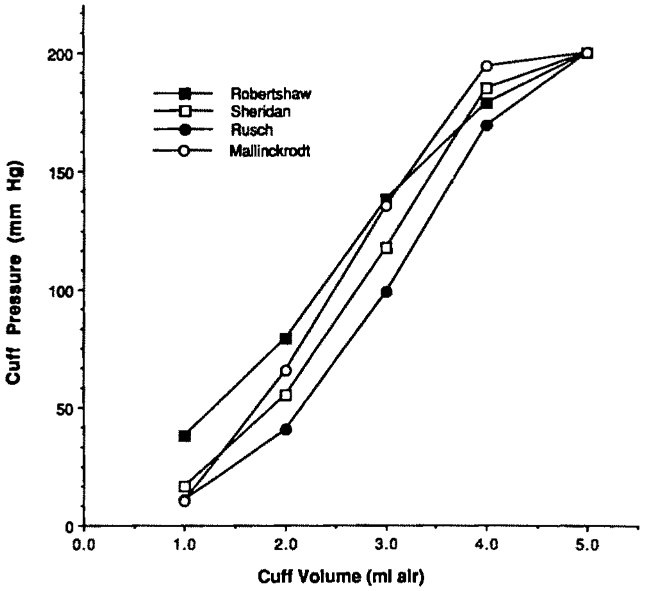

Figure 1. The pressure/volume relationships of the bronchial cuffs of the four left double-lumen tubes studied are shown. The Mallinckrodt, Rusch, and Sheridan tubes were size 41F and the red-rubber Robertshaw tube was a size larger.

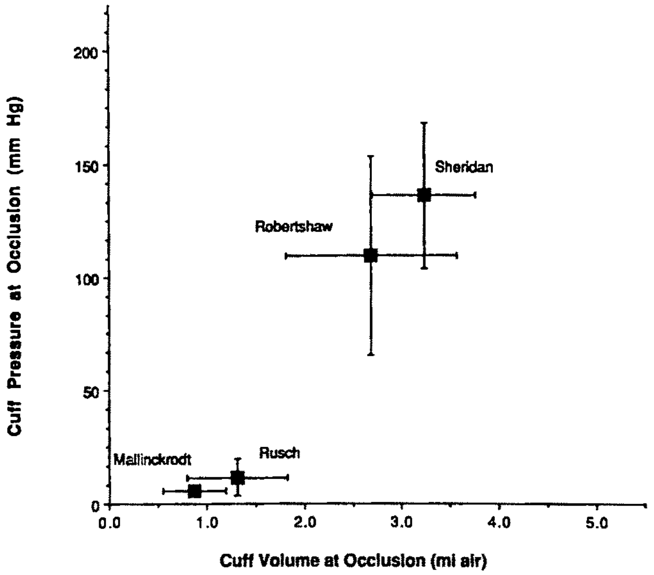

Figure 2. The bronchial cuff pressure at the volume necessary to occlude the model airway is shown. Average values for occlusion pressure (mm Hg) and occlusion volume (mL air) are shown ±1 SD. There were no significant differences in either pressure or volume between the Mallinckrodt and Rusch tubes, but both these tubes had occlusion pressures and volumes that were significantly lower ($P < 0.05$) than those of the Sheridan and Robertshaw tubes.

the cuff volume and cuff pressure at occlusion of the airway was tested by Scheffe's multiple comparisons applied to each pair of tube types. Statistical significance was considered to be achieved when $P < 0.05$.

Results

Figure 1 shows the average pressure/volume relationships of the bronchial cuffs of the four types of DLTs studied. Two milliliters of air resulted in a pressure of <80 mm Hg in all three PVC DLTs as well as in the red-rubber Robertshaw DLT. An additional 1 mL of air (total 3 mL) caused pressure to increase to 100 mm Hg or more in the bronchial cuffs of all four DLTs.

The important relationship is the pressure generated at the minimal volume necessary to occlude the airway. Occlusion pressures were <20 mm Hg for the Rusch and Mallinckrodt tubes at bronchial cuff volumes of <1.5 mL (Figure 2). There were no differences in the occlusion cuff volume nor in occlusion pressure between these two tubes. The Sheridan bronchial cuff sealed the airway at approximately 135 mm Hg and the red-rubber Robertshaw DLT required 110 mm Hg to seal the airway. There were no statistical differences in volume to occlusion nor to occlusion pressure when these two tubes were compared with each other. Occlusion volume and pressure were both significantly higher ($P < 0.05$) with the Sheridan or Robertshaw tubes than with the Rusch and Mallinckrodt DLTs.

Discussion

DLTs are a useful adjunct in thoracic surgery and their popularity has continued to increase since the introduction of PVC models, which offer important advantages with regard to ease of positioning and safety when compared with older, red-rubber DLTs (3).

Neto (4) compared 24 patients intubated with an unspecified PVC tube and 26 patients intubated with a red-rubber left Carlens DLT. Immediately after intubation, the PVC bronchial cuff pressure was 56 ± 21 mm Hg compared with 130 ± 41 mm Hg for the Carlens cuff. He concluded that because PVC tubes produced lower pressures, the risk of damage to the bronchus can be decreased by the use of PVC DLTs. Unfortunately, he failed to note information about the type and size of the tubes used in his study and what cuff volumes were needed to "just seal" the bronchus.

Although designed as low pressure/high volume cuffs, we found that all PVC cuffs produced high and potentially dangerous bronchial cuff pressures when distended with volumes of air greater than needed to seal the model airway. At 4 mL, all PVC tubes generated pressures identical to those of the high pressure/"low" volume red-rubber DLT bronchial cuff. The pressure of the bronchial cuff of the Rusch PVC DLT remained lowest at all volumes. This result may be due to its unique roller pin shaped cuff that allows pressure to be distributed over a greater surface.

The important relationship is the bronchial cuff pressure generated at the volume needed to "just seal" the bronchus. When an appropriately sized PVC DLT is in proper position, the bronchial cuff volume should be <2 mL for the Rusch and Mallinckrodt DLTs and 3.5 mL for the Sheridan and Robertshaw tubes. Our clinical experience supports these observations. We found with Mallinckrodt PVC DLTs that when >3 mL of air is needed to prevent a leak around the bronchial cuff, the cuff is probably herniating above the carina or is entirely in the trachea (5). When larger volumes are needed, we always carefully reevaluate tube position.

There have been reports of tracheobronchial rupture from red-rubber DLTs (6–8). Although this complication is rare, PVC DLTs have also been implicated in cases of left main-stem bronchial rupture (9,10). Injury usually is the result of overdistention, in effect, changing a low pressure cuff to a high pressure cuff. Further cuff distention can occur if nitrous oxide is used due to the well known effects of this gas in closed, air containing spaces (11). Therefore, when nitrous oxide is used, the bronchial cuff should be periodically deflated to avoid excessive pressure buildup on the bronchial mucosa.

The larger the PVC DLT that can be safely placed, the better, because smaller caliber tubes require more air in the bronchial cuff to seal the airway. The outside diameter of the left endobronchial lumen is approximately the same for all three 41F PVC DLTs studied (10.6–11.5 mm) (12). We do not know why the Sheridan bronchial cuff required more air and higher occlusion pressures to seal the model than those of the other PVC DLTs.

The outside diameter of the equivalent sized rubber Robertshaw tube is larger and the distal endobronchial tube is oval, unlike the more rounded bronchial portion of the PVC DLT. The bulkier rubber tube required a relatively large volume to seal the airway although the model bronchus was almost filled by the body of the tube itself. The cuff of the red-rubber tube is approximately twice as long as the PVC tubes, which may be one reason why it requires more air (13). In addition, high pressure cuffs such as the bronchial cuff of the the red-rubber tube have a tendency to dilate asymmetrically, so greater volumes may be needed to effect a seal (14).

Although mucosal ulceration, tracheomalacia, tracheoesophageal fistula, tracheal stenosis, and airway rupture have all been associated with low volume/high pressure tube cuffs, excessive lateral tracheal-wall pressure may not account for all the damage (14). Uneven distention of the bronchial cuff could drive the tip of the endobronchial tube lumen into the wall of the airway increasing the risk of airway laceration. Older, reusable red-rubber DLTs have increased stiffness and tube tip irregularities, which could cause further trauma during intubation.

The described considerations coupled with our documentation of the high pressures needed to occlude our model with the reusable Robertshaw tube suggest that disposable, low pressure PVC DLTs are safer. In our study model, two of the three PVC bronchial cuffs exerted very low pressures when inflated with a volume of air needed to seal the model airway, suggesting that the risk of ischemic pressure injury to the bronchus should be less if these tubes are used properly.

References

1. Dobrin P, Canfield T. Cuffed endotracheal tubes: mucosal pressure and tracheal wall blood flow. Am J Surg 1977; 133:562–5.
2. Sabiston DC Jr. Textbook of Surgery, 10th ed. Philadelphia: WB Saunders, 1972:2011.
3. Burton NA, Watson DC, Brodsky JE, et al. Advantages of a new polyvinyl chloride double-lumen tube in thoracic surgery. Ann Thorac Surg 1983;36:78–84.
4. Neto PPR. Bronchial cuff pressure: comparison of Carlens and polyvinylchloride (PVC) double lumen tubes. Anesthesiology 1987;66:255–6.
5. Brodsky JB. Complications of double-lumen tracheal tubes. In: Bishop MJ, ed. Consequences of Endotracheal Intubation. Problems in Anesthesia, Vol. 2. Philadelphia: J.P. Lippincott, 1988:292–306.
6. Guernelli N, Bragaglia RB, Briccoli A. et al. Tracheobronchial ruptures due to cuffed Carlens tubes Ann Thorac Surg 1979; 28:66–8.
7. Heiser M, Steinberg JJ, MacVaugh H, et al. Bronchial rupture, a complication of use of the Robertshaw double-lumen tube. Anesthesiology 1979;51:88.
8. Foster JMG, Lau OJ, Alimo EB. Ruptured bronchus following endobronchial intubation—a case report. Br J Anaesth 1983; 55:687–8.
9. Burton NA, Falls SM, Lyons T, et al. Rupture of the left mainstem bronchus with a polyvinyl chloride double-lumen tube. Chest 1983;83:928–9.
10. Wagner DL, Gammage GW, Wong ML. Tracheal rupture following the insertion of a disposable double-lumen endotracheal tube. Anesthesiology 1985;63:698–700.
11. Brodsky JB, Shulman MS, Mark JBD. Airway rupture with a disposable double-lumen tube. Anesthesiology 1986;64:415.
12. Benumof JL, Partridge BL, Salvatierra C, et al. Margin of safety in positioning modern double-lumen endotracheal tubes. Anesthesiology 1987;67:729–38.
13. Benumof JL. Improving the design and function of double-lumen tubes. J Cardiothorac Anesth 1988;2:729–33.
14. Carroll R, Heden M, Safar P. Intratracheal cuffs: performance characteristics. Anesthesiology 1969;31:275–81.

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Intravenous Ranitidine Antagonizes Intense Atracurium-Induced Neuromuscular Blockade in Rats

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LAW SC, RAMZAN IM, BRANDOM BW, COOK DR. Intravenous ranitidine antagonizes intense atracurium-induced neuromuscular blockade in rats. Anesth Analg 1989;69:611–3.

The neuromuscular action of ranitidine, an H_2-receptor antagonist, was investigated by determining its effect on atracurium-induced neuromuscular blockade in urethane-anesthetized and mechanically ventilated male Sprague–Dawley rats. An intravenous bolus and an infusion of atracurium were administered to produce a stable 93 ± 5% ($n = 11$) neuromuscular blockade as judged by tibialis anterior muscle twitch response. Ranitidine administered as a 1, 5, or 10 mg/kg normal body weight IV bolus during continuous atracurium infusion produced marked antagonism of neuromuscular paralysis. The percentage of antagonism (25 ± 9%; $n = 4$; 53 ± 19%, $n = 4$; and 79 ± 9%, $n = 3$, respectively) was linearly related to the dose of ranitidine ($r = 0.86$, $P < 0.05$). These results suggest that IV ranitidine has a significant anticholinesterase action against atracurium-induced neuromuscular blockade.

Key Words: NEUROMUSCULAR RELAXANTS, ATRACURIUM. HISTAMINE, H_2 BLOCKERS—ranitidine.

Histamine H_2-receptor antagonists are widely used in modern medicine. They decrease basal and stimulated gastric acid secretion and are effective agents in the treatment of gastric and duodenal ulcers, stress ulcers, and hypersecretory states such as the Zollinger–Ellison syndrome. These drugs are also being promoted for use in clinical anesthesia as prophylaxis against gastric acid aspiration (1,2), especially cimetidine and, more recently, ranitidine.

Antihistamines, including ranitidine, possess a wide variety of pharmacologic properties unrelated to their effect on acid secretion. Besides altering hepatic drug metabolism (3) and blood flow (4), they may also interfere with renal secretion of drugs by the proximal tubules (5). Of particular importance to anesthesiologists is recent evidence that cimetidine and ranitidine can inhibit acetylcholinesterase and, at high doses, produce neuromuscular blockade (6). Because H_2-antagonists may be given to patients who will also receive neuromuscular blocking agents, there is potential for pharmacodynamic (and perhaps pharmacokinetic) interactions between these drugs. This study was thus designed to examine this potential interaction in vivo with use of an animal model by evaluating the ability of ranitidine to antagonize intense atracurium-induced neuromuscular blockade in rats.

Methods

This study was performed according to institutional guidelines for animal experimentation. Male Sprague–Dawley rats weighing 408–485 g were anesthetized briefly (approximately 10 min) with diethyl ether followed by IV urethane (1.25 g/kg normal body weight). Urethane was used because it does not interfere with neuromuscular transmission, as do potent inhalational agents or even barbiturates (7). Additional injections of urethane were given when clinically indicated. Venous and arterial cannulae were inserted, and a tracheostomy was performed. The animals were ventilated with 100% oxygen with use of a Harvard small animal ventilator. Rectal temperature was maintained at 33.7–38.6°C with use of a heating pad and a heating lamp. Electrocardiography (ECG) was continuously monitored. The anterior tibialis muscle was exposed and coated with

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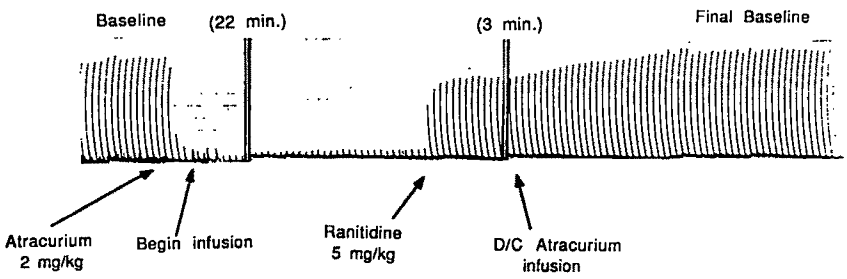

Figure 1. Example of a typical experiment. Neuromuscular blockade is achieved after atracurium IV bolus and infusion. Ranitidine (5 mg/kg) quickly antagonizes the block and a final baseline is obtained after the atracurium infusion is discontinued.

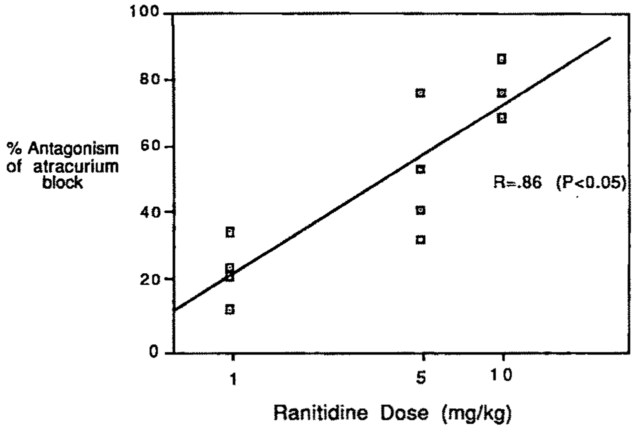

Figure 2. Dose-response curve for ranitidine antagonism of 84–98% neuromuscular block produced by a continuous infusion of atracurium.

liquid paraffin. The tendon of the anterior tibialis muscle was severed and attached to a Grass FT-03 transducer. A Grass S-48 stimulator was used to stimulate supramaximally the isolated sciatic nerve with 0.2-msec square waves at a frequency of 0.1 Hz. A polygraph recorder was used to record the mechanical twitch response.

After the surgical preparation, baseline twitch response was recorded until it became stable for 3–5 min. Atracurium was then administered as a 2 mg/kg IV bolus followed by a constant-rate infusion at about 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to obtain a neuromuscular blockade of 84–98%. Ranitidine was then administered as a 1, 5, or 10 mg/kg bolus through a catheter not being used for the continuous atracurium infusion. After observation of ranitidine's effect, the atracurium infusion was terminated followed by spontaneous recovery from neuromuscular blockade. Data were excluded from the final analysis if the final twitch height failed to reach >80% of the initial baseline.

To determine the dose-response relationship, we calculated the percentage of antagonism as

$$\frac{\text{Preranitidine block(\%)} - \text{Postranitidine block(\%)}}{\text{Preranitidine block(\%)}} \times 100.$$

Table 1. Reversal of Atracurium-Induced Neuromuscular Paralysis with Ranitidine in Rats

Ranitidine dose (mg/kg)	n	Neuromuscular paralysis (%)		Reversal (%)
		Preranitidine	Postranitidine	
1	4	97 ± 2	73 ± 10	25 ± 9
5	4	95 ± 2	45 ± 18	53 ± 19
10	3	91 ± 6	20 ± 9	79 ± 9

These values are expressed in reference to the baseline twitch response obtained before atracurium administration. The percentage of antagonism versus logarithm of the dose was analyzed with a least-squares linear regression. Statistical significance was assumed at $P < 0.05$.

Plasma ranitidine concentrations were measured in three rats approximately 1 min following the injection of 1 mg/kg ranitidine. Arterial blood samples were heparinized and centrifuged; separated plasma was stored at −20°C until assayed for ranitidine. Ranitidine was measured by high-pressure liquid chromatography (HPLC) and an ultraviolet (UV) detector.

Results

The results of a typical experiment are shown in Figure 1. A constant infusion of atracurium produced a steady level of intense neuromuscular paralysis, which was antagonized by intravenous ranitidine. After ranitidine was administered, rapid antagonism of neuromuscular blockade was observed within 30 sec. During the injection of ranitidine, occasional premature ventricular contractions were noted in some animals. The overall ranitidine effect on neuromuscular blockade was linearly correlated to the administered dose (Figure 2). Table 1 is a summary of the raw data. Injection of ranitidine vehicle alone did not affect neuromuscular function. A two-tailed t-test demonstrated that the antagonism produced by the lowest ranitidine dose (1 mg/kg) was significantly different from that by the baseline. The plasma concentration 1 min after injection of ranitidine averaged 3.5 ± 1.9 $\mu g/mL$.

Discussion

More than 60 million people have been treated with histamine H_2-receptor antagonists since the introduction of cimetidine in 1976 and of ranitidine in 1981 (3). H_2-receptor antagonists are widely used as prophylaxis against aspiration pneumonitis. In some centers, the administration of ranitidine to outpatients as a preoperative medication has become routine.

Cimetidine inhibits acetylcholinesterase (8). In vitro studies have shown low concentrations of H_2-receptor antagonists to be inhibitors of acetylcholinesterase, whereas higher concentrations produce neuromuscular blockade secondary to channel blockade (9,6). There have been no in vivo dose-response studies to evaluate the potential antagonism of nondepolarizing neuromuscular blockade by the H_2-receptor antagonists. Previous evidence shows that ranitidine pretreatment does not alter succinylcholine duration of action (10). This study was designed to examine a potential interaction in vivo in rats with use of ranitidine and atracurium.

At clinically relevant doses, ranitidine antagonizes intense atracurium-induced neuromuscular blockade. The degree of reversal observed in the present study was linearly related to the log-dose of ranitidine administered. The average plasma concentration after the 1 mg/kg ranitidine bolus was 3.5 μg/mL. This concentration is similar to the peak levels of 1.5–8.4 μg/mL in humans after an infusion of 50 mg ranitidine over 4 min (11). It is expected that a similar effect may be seen in humans immediately after an intravenous bolus of ranitidine during nondepolarizing neuromuscular blockade. A poorly documented case (12) has been reported of a patient who developed resistance to nondepolarizing blockade that was attributed to chronic oral administration of ranitidine and preceding surgery. However, a study (13) of patients taking ranitidine (150 mg) or cimetidine (400 mg orally twice a day) failed to show in vitro inhibition of acetylcholinesterase (13). A more recent study of patients taking cimetidine orally the night before and 2 hr before surgery also failed to show in vitro inhibition of acetylcholinesterase (14). Because peak concentrations following bolus administration are approximately 10 times those following oral administration (11,15), an anticholinesterase effect may be more frequently observed after IV administration. Furthermore, ranitidine is a more potent inhibitor of acetylcholinesterase than is cimetidine (6).

The present results in rats with ranitidine may be clinically relevant because they suggest that pretreatment with ranitidine to provide prophylaxis against aspiration pneumonitis may necessitate an increased dose of nondepolarizing agents to provide adequate relaxation. This effect may be of particular importance during a rapid-sequence induction of anesthesia or during operations in which even the slightest patient movement must be avoided. It is also possible that this class of drugs may eventually have potential usefulness in reversing the neuromuscular effects of nondepolarizing relaxants.

References

1. Manchikanti L, Colliver JA, Grow JB, Demeyer RG, Hadley CH, Roush JR. Dose-response effect of intravenous ranitidine on gastric pH and volume in outpatients. Anesthesiology 1986;65:180–5.
2. Moir DD. Cimetidine, antacids, and pulmonary aspiration. Anesthesiology 1983;59:81–3.
3. Rolf Smith S, Kendall MJ. Ranitidine versus cimetidine. A comparison of their potential to cause clinically important drug interactions. Clin Pharmacokinet 1988;15:44–56.
4. Feely J, Wilkinson GR, Wood AJJ. Reduction of liver blood flow and propranolol metabolism by cimetidine. N Engl J Med 1981;304:692–5.
5. Somogyi A, Gugler R. Drug interactions with cimetidine. Clin Pharmacokinet 1982;7:23–41.
6. Gwee MCE, Cheah LS, Shoon ML. Cimetidine and ranitidine: a study of competitive and ion-channel blockade in the toad isolated rectus abdominis muscle. Clin Exp Pharmacol Physiol 1986;13:613–8.
7. Zavadil AP, Dretchen KL, Raines A. Diphenylbarbituric acid: its effects on neuromuscular and spinal cord function in the cat. Epilepsia 1985;26:158–66.
8. Lee HS, Chea LS, Gwee MCE. Inhibition of acetylcholinesterase by histamine agonists and antagonists. Clin Exp Pharmacol Physiol 1985;12:613–20.
9. Chea LS, Lee SH, Gwee MCE. Anticholinesterase activity of and possible ion-channel block by cimetidine, ranitidine and oxymetidine in the toad isolated rectus abdominis muscle. Clin Exp Pharmacol Physiol 1985;12:353–7.
10. Fiamengo SA, Askari FK, Hartman GS, Riker WF Jr. Neuromuscular and cardiovascular effects of ranitidine HCl (abstr). Anesthesiology 1986;65:A297.
11. Ilett KF, Nation RL, Tjokkrosetio R, et al. Pharmacokinetics of ranitidine in critically ill patients. Br J Clin Pharmacol 1986; 21:279–88.
12. Katende RS, Dimich I. Resistance to nondepolarizing muscle relaxants in a patient treated with ranitidine. Mt Sinai J Med 1987;54:330–1.
13. Jensen JC, Gugler R. Relevant inhibition of acetylcholinesterase with H_2-receptor antagonists. Z Gastroenterol 1984; 22:109–12.
14. Kambam JR, Franks JJ. Cimetidine does not affect plasma cholinesterase activity. Anesth Analg 1988;67:64–8.
15. Roberts CJ. Clinical pharmacokinetics of ranitidine. Clin Pharmacokinet 1984;9:211–21.

614 ANESTH ANALG
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Postoperative Isolated Dysfunction of the Long Thoracic Nerve: A Rare Entity of Uncertain Etiology

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MARTIN JT. Postoperative isolated dysfunction of the long thoracic nerve: a rare entity of uncertain etiology. Anesth Analg 1989;69:614–9.

A "winged" scapula is a rare, poorly understood, and potentially disabling curiosity following anesthesia and surgery. It is produced by dysfunction of the long thoracic nerve and consequent paralysis of the serratus anterior muscle. A survey of senior anesthesiologists indicated a consistent lack of familiarity with the entity. This article presents six cases of postoperative long thoracic nerve palsy. In a literature review of 111 instances of long thoracic nerve palsy, 51 were trauma-related, 47 were either idiopathic or of debatable origin, and 13 appeared following a surgical or obstetrical procedure. Unprovable etiologic contentions were frequent. Considerations of the etiologies of postoperative long thoracic nerve palsies must include a coincidental infectious neuropathy ("neuralgic amyotrophy") as a valid alternative to the assertion that a preventable injury occurred during anesthesia.

Key Words: COMPLICATIONS, LONG THORACIC NERVE PALSY. NERVES, LONG THORACIC—postoperative palsy.

Several instances of recent litigation have focused attention on the long thoracic nerve of Bell and its potential for dysfunction following anesthetics for surgical procedures that were unrelated to the anatomic area of the nerve. Although long thoracic nerve palsy is a rare occurrence (1), it produces paralysis of the serratus anterior muscle and "winging" of the scapula. The cosmetic and functional liability that results may last for many months and is distressing to the patient. Appearance of such a surprising entity postoperatively has frequently led to corrosive accusations about who was responsible.

A review of the anesthesia literature reveals a paucity of information about this condition. Responses from an informal survey of senior anesthesiologists across the nation indicate almost no recognition of the problem (DC Boals, personal communication). This article presents several instances of postanesthetic long thoracic nerve palsy, reviews pertinent literature, and seeks an etiologic perspective that is more balanced than the current tendency to castigate automatically the anesthesiologist when the condition occurs.

Case Reports

The following reports have been derived from material that permitted acceptable assessment of details. Two additional instances are known as anecdotes but are not recounted here because details were not available for evaluation.

1) During an endotracheal anesthetic, a patient was placed in a flexed left lateral decubitus position for a right nephrectomy. The upside (right) arm was carefully secured, without detectable traction or compression, on an elevated soft rest that extended ventrally from the shoulder and was parallel to the sagittal plane of the body. Restraining tapes across the patient's hips kept the torso from rolling out of the lateral position. The anesthetic and nephrectomy were uneventful.

Postoperatively, the patient complained only of flank pain. He later stated that he had suppressed a new complaint of right shoulder pain at the time of discharge from the hospital on the 4th postoperative day to assure his return home. On the 5th and 6th postoperative days, while at home on minimal activity, he complained of an increasingly intense, dull, throbbing ache located diffusely about his right shoulder. On about the 7th postoperative day, a relative noted that the medial border of his right scapula was unusually prominent.

Nine days after the nephrectomy, the surgical

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wound was reopened to drain a hematoma. The urologist deemed the shoulder pain to be referred from the hematoma site in the ipsilateral flank. However, a consultant declared that an "injury" had occurred as the result of faulty transport, handling, or positioning of the patient at the time of the nephrectomy.

2) A healthy, athletic woman outpatient underwent an uncomplicated general anesthetic while supine for a surgical procedure on a knee. She was alert and relatively pain free on discharge from the recovery unit. Within the next 48 hr, she developed incapacitating pain in the area of her right shoulder. Scapular winging was noted several days later. After almost 2 years, it had incompletely resolved despite physiotherapy.

3) An outpatient who received a general anesthetic spent about 30 min in the low modification of the lithotomy position used by urologists for cystoscopic procedures (DC Boals, personal communication). He moved himself onto the cystoscopy table. His right arm was alongside his trunk and relaxed; the left arm, containing the intravenous infusion line, was extended on an armboard. The anesthesia and surgery were uneventful. At the end of the procedure, he was moved to a transport cart and during the recovery room stay had no complaint of arm or shoulder pain. He returned home and slept for several hours. On awakening he experienced right shoulder and upper arm pain. Four or five days later, he had an evident right long thoracic nerve palsy with winging of the right scapula.

4) The wife of a physician had an uneventful general anesthetic and hysterectomy in the supine position (RJ Rose, personal communication). No head down tilt or shoulder braces were involved. Postoperatively, she developed transient severe right shoulder pain followed by scapular winging. Recovery was apparently complete by the 8th postoperative month. Of interest is the fact that an offspring subsequently developed long thoracic nerve dysfunction secondary to wearing a backpack.

5) A woman received an uneventful general endotracheal anesthetic to permit a knee procedure while in the supine position. She was unresponsive from residual anesthesia when transferred to the recovery facility and initially needed jaw support to assure her airway. After arousal, she complained only of pain at the operative site and received minimal analgesia before transfer to her hospital room. Some time afterward, she experienced pain in her right neck, right scapular region, and upper arm; scapular winging followed. She subsequently has contended that the pain began in the recovery unit although no mention of it exists in the nursing notes. A charge was made that fasciculation consequent to the administration of intravenous succinylcholine injured the long thoracic nerve.

6) A young parturient had an epidural anesthetic administered while in the left lateral decubitus position with her lower extremities flexed to facilitate needle placement (2). As she maintained that posture, she experienced pain in her right (upside) shoulder and neck that disappeared when she was returned supine. Anesthesia was adequate and uncomplicated; delivery was uneventful. The next day, while ambulating and combing her hair, she noted weakness of her right shoulder with winging of her scapula and limited abduction of the right arm. Complete recovery occurred with conservative therapy in 6 months. The patient held the epidural anesthetic responsible for her painful upper extremity. The obstetrician, however, believed that the triggering factor was the postural neck pain that occurred briefly in the lateral position and was relieved by returning supine.

Pertinent Anatomy and Function

The long thoracic nerve was first described in 1827 by Sir Charles Bell who called it the "external respiratory nerve" (3). It arises immediately from spinal roots (anterior branches of C-5, 6, and 7) that form the brachial plexus. In rare instances, the C-8 root also contributes fibers (4). It is long (24–30 cm), unbranched until reaching its destination, free of sensory fibers, and serves as the sole innervation of the serratus anterior muscle (Figure 1).

Horwitz and Tocantins (4) dissected the nerve in 100 cadavers. The fibers from C-5 and C-6 roots usually pass through the substance of the scalenus medius muscle to unite with the C-7 component just beyond the lateral border of the middle scalene or on the surface of the posterior scalene. The C-7 portion (and fibers from C-8, if present) runs with the brachial plexus between the anterior and middle scalene muscles until joining the C-5 and 6 contribution. (Fibers of C-5 root that innervate the rhomboid also pass through the scalenus medius [5] but are not components of the long thoracic nerve.) With minor variations, the formed nerve then descends beneath the brachial plexus, passes close to the subscapular and subcoracoid bursae, continues down the anterolateral aspect of the chest wall, and gives off branches only to the various digitations of the serratus anterior. As it crosses the second rib, it lies medial to the coracoid process.

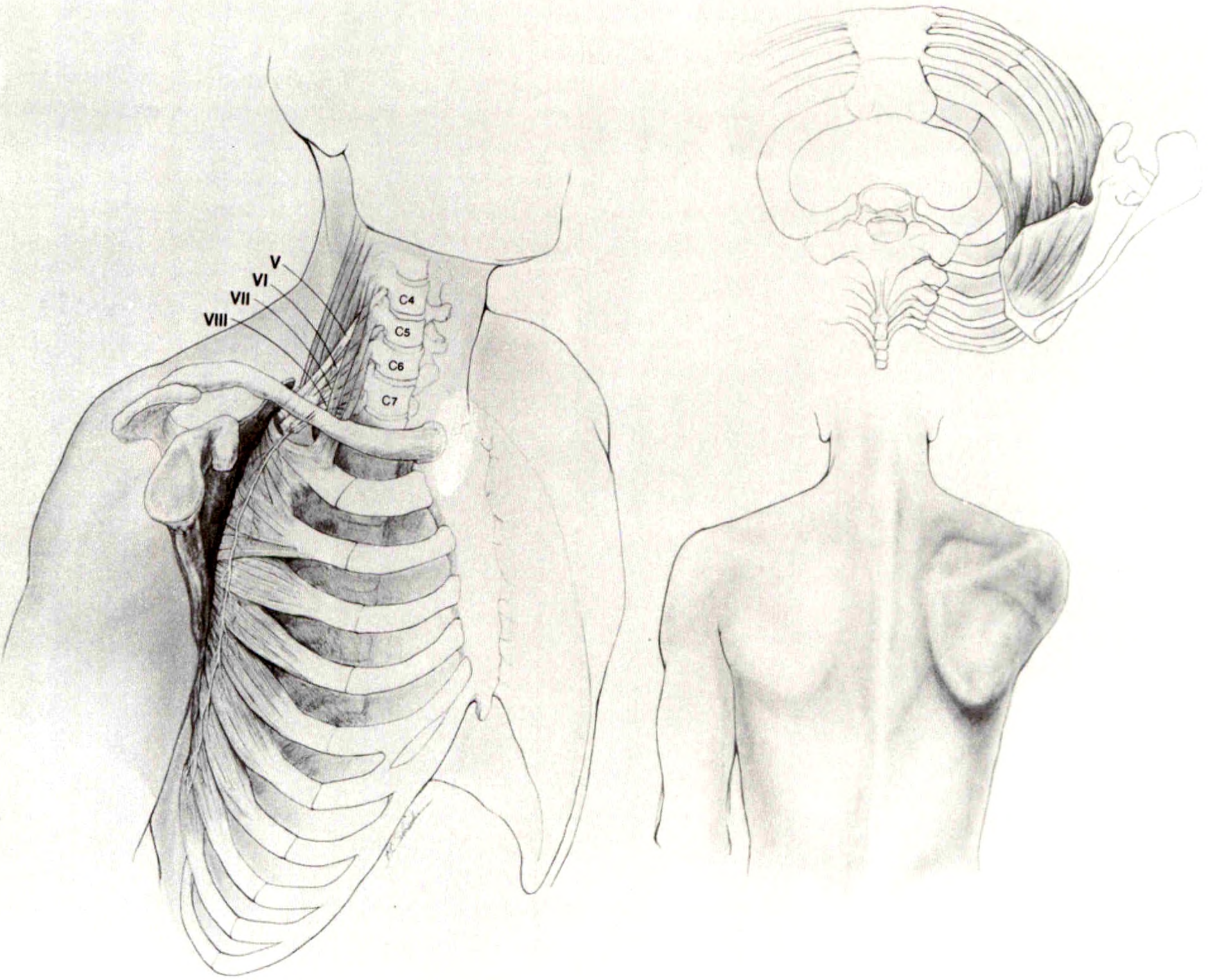

Figure 1. **Left**, the course of the long thoracic nerve of Bell from roots C-5, C-6, and C-7 of the brachial plexus, emerging between the anterior and middle scalene muscles to travel down the chest wall to the several slips of the serratus anterior muscle. **Upper right**, caudad view of the upper thoracic cage showing the slips of the serratus anterior muscle arising from lateral ribs and inserting on the deep surface of the vertebral edge of the scapula. **Lower right**, scapular winging caused by scalenus anterior palsy and accentuated by upper extremity being extended ventrally and pressed against a vertical surface.

The serratus anterior is a broad, flat muscle formed by multiple digitations arising from the upper eight or nine ribs in the midaxillary line and attaching to the ventral surface of the scapula along its vertebral aspect. Gregg et al. (5) identified three functional components of the muscle: 1) A superior cylindrical mass that attaches to the superiomedial border of the scapula and anchors the arm during its overhead rotation. In about 5% of the population (4), a separate nerve arises from the C-5 root to innervate this portion. 2) A long, thin, wide, intermediate band that connects the third, fourth and fifth ribs with the vertebral border of the scapula and draws the scapula forward. 3) The lower five slips from the sixth through the tenth ribs that converge on the lower angle of the scapula to rotate the inferior angle of the scapula upward and laterally across the chest wall. About 5% of the population (4) have separate intercostal innervation for this part of the muscle.

If the scapula is fixed by holding onto an object or by pressing the arms against something, the serratus anterior may act as an accessory inspiratory muscle by elevating the ribs. This function is evident in asthmatics who hold onto a bedrail and in runners who bend over and press their arms against their thighs to catch their breath after a race (5). It also apparently explains the ancient name of the long thoracic nerve as the "external respiratory nerve" (3).

When serratus anterior function is impaired, the vertebral border of the scapula protrudes dorsomedially (hence the term "winging"), the shoulder droops, and the arm cannot be raised beyond 90° when extended laterally. If the arm is used to attempt to push the thorax dorsally away from a vertical surface (or, as in push-ups, a horizontal one), the scapular winging is accentuated.

Discussion

Scapular winging was first reported by Velpeau in 1825 (6). Skillern (7) proposed its surgical correction in 1913 and Thorek reported a postoperative occurrence in 1926 (8). Little new information was added until 1938 when Horwitz and Tocantins (4,9) dissected the long thoracic nerve in 100 cadavers. They thought that trauma to the nerve was a major etiologic factor in its dysfunction. Distraction of the shoulder from the neck (a caudad thrust of the shoulder or a contralateral agulation of the head and neck, or both) in their specimens put the nerve on tension and they recognized the potential for a traction injury. Also, they speculated 1) that scalenus spasm or injury might compress intramuscular fibers of the nerve; 2) that angulation of the nerve trunk as it crossed the second rib and its overlying heavy musculature might be injurious; 3) that, if the scapula was forced medially, the nerve could be trapped between the coracoid process and the second rib, particularly in the cases in which the nerve roots emerged from the posterior border of the middle scalene muscle; and 4) that close association of the nerve with four bursae (the subscapular, accessory subscapular, subcoracoid, and supracoracoid) might permit nerve compression if these bursae were inflamed. They commented (4,9) on the possibility that prolonged maintenance of the supine position during obstetrical procedures and surgical operations, as well as by chronically bedridden patients, might injure the nerve, particularly if adjacent bursae become inflamed. They noted that sleeping prone or on the contralateral side relieved the shoulder pain. They also stated that there were enough morphologic variations of the formation and course of the nerve to explain why "identical traumata in different individuals only infrequently result in this lesion."

The earliest attention by an anesthesiologist to isolated serratus anterior palsy came from Paul Lorhan at the University of Kansas. In a surgical journal (10), he noted potential sources of trauma to the nerve 1) in the placement of shoulder braces to stabilize the Trendelenburg position; 2) in neck and arm stress when an unconscious patient is moved between operating table and transport cart; and 3) in finger pressure on the lateral neck or forced rotation of the head to one side when a difficult face or jaw configuration complicates the effective fit of an anesthesia face mask. The anesthesia literature itself was devoid of reference to the palsy until the report of Hubbert in 1988 (2). It was not mentioned in either the classic article of Jackson and Keats about injuries to the brachial plexus (11) or in a recently revised text concerning the positioning of patients for surgery (12).

An early and extensive review of isolated paralysis of the serratus anterior muscle by Johnson and Kendall at Johns Hopkins Hospital appeared in 1955 (13). They reviewed 111 cases from the literature and added 20 of their own. Eighty-three percent of their cases were right sided. In a few instances, the condition began painlessly; however, the usual onset involved aching or burning in the shoulder with sharper pain, often intense, radiating down the arm and/or around to the scapula. In 24–48 hr, the shoulder was weak and drooped forward, it fatigued easily, and scapular winging was evident (worsened by push-ups). The antagonistic musculature (rhomboids and pectoralis minor) was tight and frequently painful. Their etiologic statistics were 35 with acute trauma to the neck and shoulder; 16 with recurrent trauma such as sports (archery, tennis) or wearing a knapsack; 13 who had exposure to cold; 13 with an ongoing or recent infection; 8 who had recent injection of serum or drug, possibly an allergic reaction; 7 who had recent surgery; 6 who had recent obstetrical delivery; and 13 who were idiopathic. They noted the similarity of their etiologic data to those of other isolated neuropathies, like the facial palsy of Bell, and speculated on the involvement of a nonspecific "neuritis."

Bora et al. (14) showed that a nerve can be elongated by as much as 10% of its rest length without loss of its function, but that further stretching produces neurapraxia (a conduction defect without structural degeneration). Anatomic studies by Gregg and associates (5) at the University of Pennsylvania in 1979 revealed the vulnerability of the long thoracic nerve to a traction injury. By turning the head of a fresh cadaver away from one shoulder and raising the ipsilateral arm overhead (a motion common to bowling and archery), they could easily double the length of the segment of the nerve that lay between its points of fixation in the middle scalene muscle and the multiple slips of the serratus anterior. A resultant neuropathy was implied. However, they discounted muscle spasm of the middle scalene as a cause of long thoracic nerve injury because C-5 root fibers to the rhomboid also pass through the middle scalene and rhomboid dysfunction is not a common component of serratus anterior palsy. Gregg's group also tested the proposal that an isolated long thoracic nerve injury could be produced by crushing the nerve between the clavicle and the second rib but found that the maneuver always simultaneously damaged the adjacent brachial plexus.

Foo (15) reviewed 20 cases of scapular winging, the majority of which had no definable etiology. He discounted the stretched nerve hypothesis, believing that a nerve of this length should have acceptable elasticity. He also noted that traction injuries of the brachial plexus were not invariably involved with palsies of the long thoracic nerve. Because of the high incidence of idiopathic onsets and the tenuous assumptions that identified many of the supposed causative factors, Foo thought that the most likely etiology was "neuralgic amyotrophy." The term had been introduced by Parsonage and Turner (16) to describe paralytic brachial neuritis in 136 symptomatic military personnel, 30 of whom had isolated paralysis of the serratus anterior muscle. In 99 comparable neuropathies examined by Tsairis and associates at Mayo Clinic (17), biopsies of long thoracic nerves showed diffuse axonal degeneration. The differential diagnosis of neuralgic amyotrophy (18) (neuralgia and progressive muscle atrophy) includes poliomyelitis, motor neuron disease, diabetic amyotrophy, spinal muscular atrophy, muscular dystrophy, and cervical spondylosis. Its onset is spontaneous and usually painful with flaccid paralysis of the involved musculature appearing after about 2 weeks. Acceptable degrees of recovery may require up to 2 years. Apparently there is also a rare familial form of neuralgic amyotrophy (19) associated with childhood, short stature, hypotelorism, cranial nerve palsies, and a tendency to recur. Foo (15) also noted that adequate explanations were not available either for the predilection for neuralgic amyotrophy to involve the upper branches of brachial plexus or for its right-sided predominance even in left-handed people.

Say and Donegan (20) reported a 10% occurrence of long thoracic nerve palsy after its operative exposure during radical mastectomies and Pugliese et al. (21) added an unusual occurrence of onset of dysfunction of the nerve after radiation therapy. Rarely a congenital absence of the serratus anterior results in an alar scapula at an early age (22).

Opportunities certainly exist perioperatively for the occurrence of trauma to the long thoracic nerve (cases 1 and 6, concerning the neck in the lateral position) even when the surgical procedure involves another anatomic location. Suggestions made by Lorhan in the mid-1940s are still valid (10). Movement of a patient onto and off of the operating table may contribute to nerve injury. In light of the possibilities for traumatic long thoracic nerve palsy, one wonders why the malady is so infrequent. Nevertheless, the lack of information about the issue among senior anesthesiologists (DC Boals, personal communication) emphasizes the fact that, with usual and acceptable patient care, the odds are so great against encountering an episode of isolated long thoracic nerve dysfunction due to perioperative trauma that statistical assessment and accurate definition of the moment of injury is virtually impossible.

It is also possible to have a postoperative personal act by the patient implicated etiologically (case 3 in which the patient slept at home after surgery and awakened with the initial episode of arm pain).

Injury to those fibers of the long thoracic nerve that pass through the middle scalene muscle has been alleged to be due to fasciculations that occur during the onset of a depolarization block of the myoneural junction. That this is not probable is indicated by the fact that fibers to the rhomboid also pass through the middle scalene muscle, although rhomboid paralysis is not part of the findings in long thoracic nerve palsy.

An examination of the literature regarding the speculated causes of isolated long thoracic nerve palsy raises questions about the validity of some of the assumptions. Why should exposure to cold (13 of 111 of the Johnson and Kendall cases [13]) result in a single nerve lesion, and why this nerve? Why should a recent injection of a serum or drug (8 of 111) cause the specific mononeuropathy when other indexes of "allergic reactions" were apparently not evident? If the idiopathic group (13 of 111) is added to these contemplations, 30% of the cases (13 + 13 + 8 = 34 of 111) in that reported series (13) have uncertain etiologies. The potential for a time-related and coincidental neuropathy becomes apparent from these questions and must be factored into any discussion of etiology caused by a specific event. Consider the hypothetical situation in which an otherwise healthy gentleman purchases a new suit and dons it to visit a client. During the interview, he becomes aware of the early signs of Bells palsy of his facial nerve. Is the etiologic agent the suit? Is it the client? Or is the example yet another instance of an idiopathic onset of a neuropathy of uncertain etiology? Although not negating the potential for perioperative trauma to the long thoracic nerve, the parallel between that scenario and the postoperative appearance of palsy of a long thoracic nerve is valid. The parallel also supports the presumption of Foo (15) about neuralgic amyotrophy.

Conclusions

Isolated palsy of the serratus anterior muscle due to dysfunction of the long thoracic nerve is so rare that it is poorly understood and is open to faulty etiologic conclusions. For undetermined reasons, the palsy usually involves the muscle and nerve on the right side. A familial susceptibility may exist. Appropriate therapy can aid recovery. In most instances, nontraumatic forms of the palsy improve or resolve completely in 6 to 24 months with conservative treatment.

Neck trauma, such as an acute blow to the area of the middle scalene muscle, lateral angulation of the neck away from the affected shoulder, or forced caudad motion of the shoulder, has the potential to contuse or stretch the long thoracic nerve and cause an isolated palsy of the serratus anterior muscle.

A traction injury to the brachial plexus does not necessarily involve the long thoracic nerve. Similarly, an injury to the long thoracic nerve can occur without damage to the brachial plexus. Spasm or fasciculations of the middle scalene muscle are unlikely causes of long thoracic nerve palsy.

The lateral decubitus position has been associated with serratus anterior palsy, perhaps because of the upside long thoracic nerve being stretched by lateral angulation of the neck and head away from the upside shoulder.

The supine and lithotomy positions have been associated with serratus anterior palsy after surgery, delivery, and prolonged bed rest. A definite cause is obscure and the contribution of bursitis about the shoulder to compression of the nerve is speculative at best.

By exclusion, and by etiologic inference, evidence exists for the presence of an independent neuropathy in a significant proportion of cases of long thoracic nerve palsy. This fact implies that the onset of the condition could be unrelated to, but coincidental with, a carefully conducted and uneventful anesthetic, operation, or delivery. Importantly, recognition of that fact frees the surgeon, obstetrician, and anesthesiologist from automatic presumptions of having negligently inflicted an injury on a patient should such a postoperative or postpartum palsy occur.

References

1. Overpeck DO, Ghormley RK. Paralysis of the serratus magnus muscle. JAMA 1940;114:1994–7.
2. Hubbert CH. Winged scapula associated with epidural anesthesia. Anesth Analg 1988;67:418–9.
3. Bell J, Bell C. Anatomy and Physiology of the Human Body, 5th ed. Vol. 1. New York: Collins, 1827.
4. Horwitz MT, Tocantins LM. An anatomic study of the role of the long thoracic nerve and the related scapular bursae in the pathogenesis of local paralysis of the serratus anterior muscle. Anat Rec 1938;71:375–85.
5. Gregg JR, Labosky D, Harty M, et al. Serratus anterior paralysis in the young athlete. J Bone Joint Surg 1979;61:825–32.
6. Velpeau AALM. Traite d'anatomie chirurgicale ou anatomie des regions consideree dans ses rapports avec la chirurgie. Vol. 1. Paris: Crevot, 1825:303.
7. Skillern PG Jr. Serratus magnus palsy with proposal of a new operation for intractable cases. Ann Surg 1913;57:909–15.
8. Thorek M. Compression paralysis of the long thoracic nerve following an abdominal operation. Am J Surg 1926;40:26–7.
9. Horwitz MT, Tocantins LM. Isolated paralysis of the serratus anterior (magnus) muscle. J Bone Joint Surg 1938;20:720–5.
10. Lorhan PH. Isolated paralysis of the serratus magnus following surgical procedures. Arch Surg 1947;54:656–9.
11. Jackson L, Keats AS. Mechanisms of brachial plexus palsy following anesthesia. Anesthesiology 1965;26:190–4.
12. Martin JT, ed. Positioning in Anesthesia and Surgery, 2nd ed. Philadelphia: WB Saunders, 1987.
13. Johnson JTH, Kendall HO. Isolated paralysis of the serratus anterior muscle. J Bone Joint Surg (Am) 1955;37A:567–74.
14. Bora FW Jr, Pleasure DE, Didizian NA. A study of nerve regeneration and neuroma formation after nerve suture by various techniques. J Hand Surg 1976;1:138–43.
15. Foo CL. Isolated paralysis of the serratus anterior: a report of 20 cases. J Bone Joint Surg 1983;65B:552–6.
16. Parsonage MJ, Turner JWA. Neuralgic amyotrophy: the shoulder-girdle syndrome. Lancet 1948;i:973–8.
17. Tsairis P, Dyck PJ, Mulder DW. Natural history of brachial plexus neuropathy: report on 99 patients. Arch Neurol 1972; 27:109–17.
18. Neuralgic amyotrophy—Still a clinical syndrome (editorial). Lancet 1980;ii:729–30.
19. Dunn HG, Daube JR, Gomez MR. Heredofamilial brachial plexus neuropathy (hereditary neuralgic amyotrophy with brachial predilection) in childhood. Dev Med Child Neurol 1978;20:28–46.
20. Say C, Donegan W. A biostatistical evaluation of complications from mastectomy. Surg Gynecol Obstet 1974;138:370–6.
21. Pugliese GN, Green RF, Antonacci A. Radiation-induced long thoracic nerve palsy. Cancer 1987;60:1247–8.
22. Levin SE, Trummer MJ. Agenesis of the serratus anterior muscle: a cause of winged scapula. JAMA 1973;225:748.

Incidence of Venous Air Embolism during Cesarean Section Is Unchanged by the Use of a 5 to 10° Head-Up Tilt

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KARUPARTHY VR, DOWNING JW, HUSAIN FJ, KNAPE KG, BLANCHARD J, SOLOMON D, ALBIN MS. Incidence of venous air embolism during cesarean section is unchanged by the use of a 5 to 10° head-up tilt. Anesth Analg 1989;69:620–3.

One hundred healthy parturients were divided at random into two demographically similar groups and were positioned for cesarean section either horizontally or flexed 5 to 10° head up, with a 15° lateral tilt. A Doppler ultrasound transducer was positioned over the fourth intercostal space parasternally. Initially, two patients received spinal, three general, and 95 epidural anesthesia. Two patients subsequently needed general for failed epidural anesthesia. Changes in Doppler heart tones (>15 sec duration) indicative of venous air embolism (VAE) were identified 15 times in 11 patients—seven in supine and four in head-up patients (no statistically significant difference). Six awake patients (three horizontal, three head-up) developed chest tightness or pain during surgery, but only one episode correlated with VAE. No patient developed breathlessness. Moderate hypotension (>10% decrease in systolic arterial pressure [SAP]) occurred in seven of 11 (63.6%) patients with, and in 26 (29.2%) of 89 patients without, VAE ($P < 0.001$). More severe hypotension (SAP <90 mm Hg) due to bleeding occurred once. We conclude that a modest (5–10°) head-up position does not influence the occurrence of VAE in patients having cesarean section. An 11% incidence of clinically insignificant VAE, although low, is still worrisome, as even small air bubbles in the circulation are potentially harmful, especially if the foramen ovale is patent. VAE during cesarean section should be anticipated and the anesthetic management planned accordingly.

Key Words: ANESTHESIA, OBSTETRIC—cesarean section. EMBOLISM, AIR—cesarean section.

Venous air embolism (VAE) occurs not infrequently during cesarean section (1,2). Though usually covert, VAE is nevertheless a potentially lethal obstetric complication (3,4). During cesarean section, the patient is usually supine with a 15° left lateral tilt. In this position, the heart is situated 10 to 15 cm below the uterus. As a result, a subatmospheric or "negative" venous pressure gradient exists between the right atrium and the uterine incision. If a head-down tilt is added, the venous pressure gradient may increase and thus magnify the risk of VAE.

Air bubbles as small as 0.1 mL in volume can be detected using a Doppler ultrasound transducer (5–7). This sophisticated, sensitive, noninvasive, and safe monitor is employed extensively in neurosurgery and other circumstances where VAE is a special hazard, for early detection of air bubbles in the heart (7). More recently, Doppler ultrasound studies have demonstrated a high incidence of VAE associated with cesarean section, 52% in one study (1) and, in another, 71% of patients having general and 39% receiving epidural anesthesia (2).

This study investigated the occurrence of VAE during cesarean section in our own practice and tested the prophylactic value of 5 to 10° head-up patient tilt during surgery as a means of reducing the risk of VAE. Head-up tilt should, in theory, diminish or eliminate the prevailing "negative" venous pressure gradient between the heart and uterus. The study was conducted in a randomized fashion with both written informed patient consent and institutional review board approval.

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Patients and Methods

One hundred healthy, normovolemic parturients presenting for either elective or emergent, but not immediate, cesarean section at term were the subjects of this study. Every patient had 30 mL of 0.3 M sodium citrate, intravenous (IV) metoclopramide 10 mg, and ranitidine 50 mg before transfer to the operating room. All patients were given 500 to 1000 mL of lactated Ringer's solution intravenously 15 to 30 min before the induction of anesthesia.

In 95 patients epidural anesthesia was induced after identification of the epidural space at the L2–3 or L3–4 level using an 18-gauge Touhy epidural needle. A 23-gauge epidural catheter was inserted through which incremental doses of lidocaine 2% with 1: 200,000 epinephrine, bupivacaine 0.5% plain, or 3% 2-chloroprocaine without epinephrine were injected. A sensory blockade level of T2–4 was achieved before surgery began. More of the same local anesthetic was administered when necessary to prolong anesthesia. All patients receiving epidural anesthesia breathed oxygen-enriched air.

In two patients spinal anesthesia with 1% tetracaine injected through a 25-gauge spinal needle was used. In five other patients general anesthesia was given—in three because of lack of time to establish regional anesthesia, and in two because epidural blockade failed. General anesthesia consisted of rapid sequence induction with injection of thiopental (3.5 mg/kg) and succinylcholine (1 mg/kg) followed by tracheal intubation. Anesthesia was maintained with 50:50 nitrous oxide in oxygen plus 0.8% isoflurane. Muscle relaxation was provided by injecting vecuronium 0.05 mg/kg intravenously.

After delivery, anesthesia was supplemented intravenously with fentanyl 50 to 200 μg. All patients received an IV infusion of oxytocin 40 IU in 1000 mL lactated Ringer's solution after delivery.

Every patient was operated upon in a 15° left lateral tilt position. Fifty patients were horizontal and 50 flexed 5 to 10° head up according to a random numbers table. Maternal arterial blood pressure was measured and recorded every 3 to 5 min using an automated oscillotonometer (Datascope Accutor model 1A). Maternal systolic arterial blood pressure was kept above 100 mm Hg by IVI ephedrine 5 to 10 mg when necessary. Electrocardiogram (Hewlett Packard 78534C monitor/terminal) and pulse and oxygen saturation (Omheda Biox 3700 pulse oximeter) were monitored continuously. Patients given general anesthesia had inspired oxygen and end-tidal carbon dioxide concentrations measured throughout anesthesia using a multigas analyzer (Datex 254 Airway Gas Monitor). Patient temperatures were monitored continuously (Mon-a-therm model 650U). By protocol, no direct questions regarding patient discomfort were asked during the procedure. However, unsolicited comments concerning chest tightness or pain, shortness of breath, or other symptoms were recorded. Times of exteriorization of uterus and hypotension were noted.

A noninvasive Doppler ultrasound (Versatone Mediasonics model D-8) transducer was placed initially over the fourth intercostal space parasternally. Optimum positioning was checked by the response to an IV bolus injection of 10 ml normal saline. The transducer was moved as needed in order to obtain the best audible Doppler signal. A positive change in Doppler heart tone indicative of VAE was defined as occurrence of "broken up" roaring change in the rhythmic "swishing" sound of the normal precordial Doppler signal lasting 15 sec or longer (1). Intravenous injections of medication were noted while observing the change in the Doppler signal. This served two purposes: it eliminated "false" positive Doppler signals unassociated with VAE, and reconfirmed proper positioning of the Doppler transducer. Ultrasound output was recorded continuously on a tape recorder for later review.

Statistical analyses included Student's *t*-test and the χ^2 test with Yates' correction for statistical analyses of parametric and nonparametric data, respectively.

Results

The two randomized study groups (horizontal vs flexed 5 to 10° head up) were demographically comparable with regard to age (25.5 ± 0.6 vs 25.5 ± 0.7 years), height (59.9 ± 1.7 vs 61.1 ± 1.2 cm), weight (181.9 ± 8.4 vs 178.8 ± 6.4 kg), gestation (39.4 ± 0.3 vs 39.3 ± 0.4 weeks), and parity (1.6 ± 0.2 vs 1.4 ± 0.2). Fifteen episodes of VAE as defined by protocol were identified in 11 patients. In four patients VAE was detected more than once. Of the 11 VAE-"positive" subjects, seven were horizontal and four head-up (no statistically significant difference).

An additional eight patients had brief changes in Doppler heart tones equivocal in nature and lasting less than 15 sec (five horizontal and three head-up). These eight subjects were considered not to have had VAE as defined.

Concerning the 11 VAE-"positive" patients, of the 15 episodes of VAE recorded, three (27%) occurred with uterine incision, two (18%) in association with fetal delivery, eight (73%) during placental extrusion, and two (18%) during uterine repair.

Nine (9.5%) of the 95 patients given regional anesthesia (eight epidural and one spinal) and two (40%) of the five patients receiving general anesthesia developed VAE. Seven of the 11 patients with VAE were horizontal (five epidural, two general) and four were head-up (three epidural, one spinal).

No patient felt breathless, but six (55%) volunteered that they felt tightness of the chest. Only one of these six had VAE. Of these, three were horizontal and three head-up. One-third of the 100 subjects studied developed modest levels of clinical hypotension (<100 but >90 mm Hg systolic arterial pressure). Seven of the 33 hypotensive episodes occurred in the 11 VAE-"positive" patients, an incidence of 64% (seven of 11 patients) vs 29% (26 of 89 patients) in subjects without evidence of VAE ($P < 0.001$). Only one patient developed a systolic blood pressure less than 90 mm Hg due to bleeding, not VAE. No patient developed oxygen desaturation (percent oxyhemoglobin saturation <95%).

Discussion

The incidence of VAE during cesarean section reported in the anesthetic literature is disturbingly high (1,2). In one study, an overall 52% incidence of VAE (46 of 89 patients) was reported. Air was detected in the heart by Doppler sonography in the 46 VAE-"positive" subjects during hysterotomy (74%), at the time of delivery (2%), during placental extrusion (13%), and with uterine repair (11%) (1). Twenty-four of the 46 (52%) patients complained of chest pain in association with VAE, and dyspnea was reported by nine (20%). Eight of these subjects complained of shortness of breath, too. Somewhat surprisingly, there were no changes in vital signs noted during these episodes of chest pain and/or dyspnea with VAE.

Another similar study reported VAE incidences of 71% (10 of 14 patients) and 39% (50 of 129 patients) delivered by cesarean section under general anesthesia and epidural analgesia, respectively (2). In 18 of the patients in this investigation, both precordial Doppler monitoring and echocardiography were used simultaneously. Five of the 18 patients (28%) had evidence of VAE, there being excellent correlation between the two methods for air embolus detection. VAE was diagnosed more than once in a number of patients. Relationships between surgical events and VAE during general and regional anesthesia, respectively, were: before uterine incision—10% and 26%; at uterine incision—30% and 26%; with delivery of the baby—0% and 6%; in association with placental extrusion—30% and 26%; during uterine closure—90% and 34%; and after the uterus was sutured—10% and 8%.

Oxygen desaturation (<95%) was associated with VAE in 20% of parturients given general anesthesia and in 8% given regional anesthesia. Only one patient in the group given an epidural anesthetic (1 of 129 patients, or 0.78%) developed chest pain and dyspnea with ventricular tachycardia, a marked decrease in oxygen saturation, and hypotension in association with VAE.

Cardiac arrest and death have followed VAE during cesarean section (3,4). It is estimated that VAE causes 1% of maternal deaths, an incidence comparable to that due to pulmonary aspiration of acid gastric content with or without failure to intubate the trachea (8). The latter complications have generated great interest among practicing obstetric anesthesiologists, often featuring in the anesthetic literature. This contrasts with the infrequent mention of, or emphasis on, the problem of VAE during cesarean section, despite repeated historical references to it (9).

We were unable to substantiate the high incidence of "definite" VAE reported by others (1,2). Nonetheless, if more than a tenth of patients undergoing cesarean section suffer detectable and sometimes multiple episodes of VAE, it is an important and disturbing clinical complication worthy of attention. Our results also differ from those of others with regard to times at which VAE occurred during cesarean section (1,2). Our highest incidence of VAE occurred with placental delivery (73%) rather than during hysterotomy (27%) or uterine closure (18%). Our findings in this regard were not unexpected, as shortly after placental separation large uterine sinuses lie exposed, open, and therefore vulnerable to air entry from a now empty uterus. Patient symptoms indicative of VAE and cardiopulmonary compromise were less troublesome and of little practical importance in the present report when compared to other studies. However, easily reversible and clinically inconsequential hypotension was not uncommon, especially with VAE. More severe hypotension was not seen.

Despite our findings of a relatively low incidence of VAE (11%) and lack of clinically significant cardiopulmonary symptoms and signs with VAE, there seems to be little room for complacency. Efforts to alleviate the risk of VAE by eliminating the "negative" venous pressure gradient between the heart and uterus using a 5 to 10° head up tilt proved unsuccessful, however. Perhaps a greater degree of head-up flexion would have been more effective, but this maneuver could interfere with surgical exposure.

Our results suggest that VAE occurs quite frequently but, fortunately, usually without major associated clinical signs and symptoms indicative of cardiopulmonary compromise. Although lethal VAE is rare in obstetrics, even small air bubbles in the circulation threaten patients with patent foramen ovale, a not uncommon abnormality (10–12). This fact should be borne in mind during cesarean section, and the anesthetic management should be planned accordingly.

Routine monitoring for VAE using Doppler ultrasound would seem wise, especially for patients likely to have a low central venous pressure, which predisposes them to significant VAE. Patients who are dehydrated due to prolonged labor or as a deliberate policy in the management of severe preeclampsia may be especially at risk, as may patients with compensated hemorrhagic shock. In these situations a multiorifice Albin–Bunegin central venous catheter should be used to allow rapid and effective removal of air from the central circulation (13,14). Epidural and spinal anesthesia without adequate volume preloading of the circulation could in theory also predispose toward VAE by lowering central venous pressure and increasing the right atrial to uterine "negative" venous pressure gradient. However, the study by Fong et al. indicates that parturients are at greater risk of clinically significant VAE under general anesthesia. This was also the trend in the present study and could be attributed to generous "volume preloading" prior to induction of epidural anesthesia.

In conclusion, we advise that the problem of VAE during cesarean section be taken at least as seriously as that of pulmonary acid aspiration and failed tracheal intubation. Further research is indicated to define more clearly those women at particular risk of serious VAE. Although we believe that our own obstetricians differ little from obstetricians in general with regard to operating methods and abilities when compared to their peers in other similar institutions, the contribution of different surgical techniques to the incidence of VAE also requires elucidation. Obstetricians and obstetric anesthesiologists alike should be both alert to the possibility of VAE occurring during cesarean section and prepared to deal with the problem.

References

1. Malinow AM, Naulty JS, Hunt CO, Datta S, Ostheimer GW. Precordial ultrasonic monitoring during cesarean delivery. Anesthesiology 1987;66:816–9.
2. Fong J, Gadalla F, Pierri MK, Koff H, Artusio JF. Incidence of venous air embolism during cesarean section. Anesthesiology 1988;69:A655.
3. Davies DE, Digwood KI, Hilton JN. Air embolism during caesarian section. Med J Aust 1980;1:644–6.
4. Younker D, Rodriguez V, Kavanagh J. Massive air embolism during cesarean section. Anesthesiology 1986;65:77–9.
5. Michenfelder JD, Miller RH, Gronert GA. Evaluation of an ultrasonic device (Doppler) for diagnosis of venous air embolism. Anesthesiology 1972;36:164–7.
6. Chang JL, Albin MS, Bunegin L, Hung TK. Analysis and comparison of venous air embolism detection methods. Neurosurgery 1980;7:135–41.
7. Albin MS, Carroll RG, Maroon JC. Clinical considerations concerning detection of venous air embolism. Neurosurgery 1978;3:380–4.
8. Robinson DA, Albin MS. Parturition and venous air embolism. Obstet Anesth Dig 1987;7:38–40.
9. Kaunitz AM, Hughes JM, Grimes DA, et al. Causes of maternal mortality in the United States. Obstet Gynecol 1985;65:605–12.
10. Clayton DG, Evans P, Williams C, Thurlow AC. Paradoxical air embolism during neurosurgery. Anaesthesia 1985;40:981–9.
11. Coleman SA, Wilson-MacDonald J. Fatal paradoxical thromboembolism during anaesthesia. Anaesthesia 1988;43:213–5.
12. Webster MWI, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM. Patent foramen ovale in young stroke patients. Lancet 1988;i.
13. Smith SL, Albin MS, Ritter RR, Bunegin L. CVP catheter placement from the antecubital veins using a J-wire catheter guide. Anesthesiology 1984;60:238–40.
14. Artru AA, Colley PS. Bunegin–Albin CVP catheter improves resuscitation from lethal venous air embolism in dogs (abstract). Anesth Analg 1986;65:S7.

ANESTH ANALG
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Effect of Rate of Injection on the Neuromuscular Block Produced by Vecuronium

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FELDMAN SA, SONI N, KRAAYENBRINK MA. Effect of rate of injection on the neuromuscular block produced by vecuronium. Anesth Analg 1989;69:624–6.

A subparalytic dose (0.015 mg/kg) of vecuronium bromide was administered to matched pairs of patients undergoing routine dental surgery under enflurane-nitrous oxide/oxygen anesthesia either as a rapid bolus injection or as a slow infusion over 5 min. It was demonstrated that bolus injection produced peak plasma levels of drug considerably greater than those following slow infusion. Time to maximum block was more rapid following bolus (368 ± 84 [SD] sec) than by infusion (615 ± 88 sec), but the maximum block produced, either demonstrated by the reduction in amplitude of T_1 from control or the T_1:T_4 ratio on the integrated electromyogram (Datex IEMG), was similar in each group irrespective of rate of injection, T_1 and T_4 referring to the first and last twitch in a train of four series.

Key Words: NEUROMUSCULAR RELAXANTS, VECURONIUM.

It can be anticipated that, following a slow infusion of vecuronium, the peak plasma level of drug would be lower than that achieved when the drug is administered as a rapid bolus injection. As a result, both the time to maximum block and the degree of neuromuscular block would be affected. This study was performed to determine the extent to which these parameters are affected by the different modes of administration.

Methods

In order to recognize the effect of small differences in receptor occupancy anticipated in this study, it was necessary to use subparalytic doses of vecuronium (1). In a pilot study it was found that in healthy young adults anesthetized with nitrous oxide/oxygen (N_2O/O_2) and 1.5% enflurane, a dose of 0.015 mg/kg produced an approximately 50% depression of T_1. This dose of drug was therefore used in this trial.

Thirteen pairs of fit young adults (ASA physical status I) presenting for removal of wisdom teeth under general anesthesia were studied. Each pair was of similar age and weight. All patients were premedicated with papaveretum and hyoscine prior to surgery. Anesthesia was induced with thiopental (4 to 5 mg/kg) through an indwelling cannula on the dorsum of the hand. The cannula was flushed with saline between injections. Anesthesia, with the patient breathing spontaneously, was maintained with N_2O, O_2, and enflurane 1.5%. After steady state anesthesia was established, an integrated electromyogram (Datex IEMG) was attached and basal readings obtained. The vecuronium was mixed freshly and made up to a concentration of 0.1 mg/mL for each pair of patients in the study. One patient in the pair was allocated, at random, to receive vecuronium (0.015 mg/kg) by rapid bolus injection and the other the same dose by slow infusion over 5 min.

The IEMG was continuously recorded and the time to maximum depression of T_1, the percentage depression of T_1, T_4, and the T_4:T_1 ratio, relative to baseline values, were recorded for each patient. In order to elicit these values, the ulnar nerve was stimulated supramaximally with repeated "train of four" stimuli (2 Hz for 2 sec at 20-sec intervals) using surface electrodes at the wrist. The evoked compound electromyogram of the adductor pollicus muscle was recorded with the Datex Relaxograph.

Blood was sampled from the opposite antecubital vein at 1-min intervals for the measurement of

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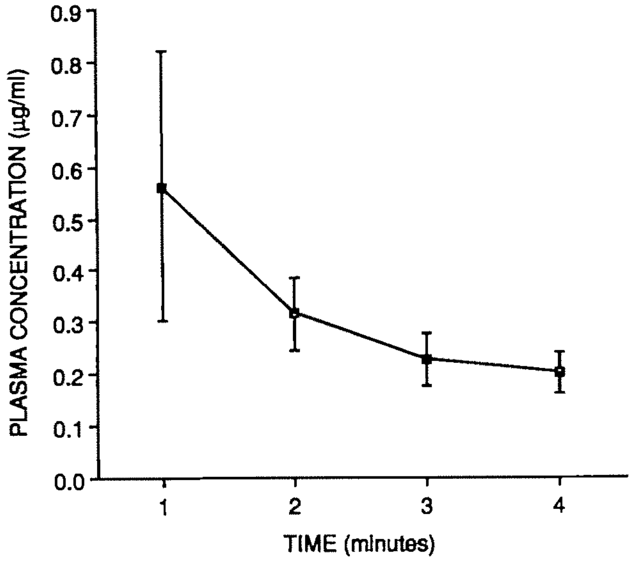

Figure 1. Plasma concentration (mean ± SD µg/mL) of vecuronium as a function of time in minutes following the IV bolus injection of 0.015 mg/kg.

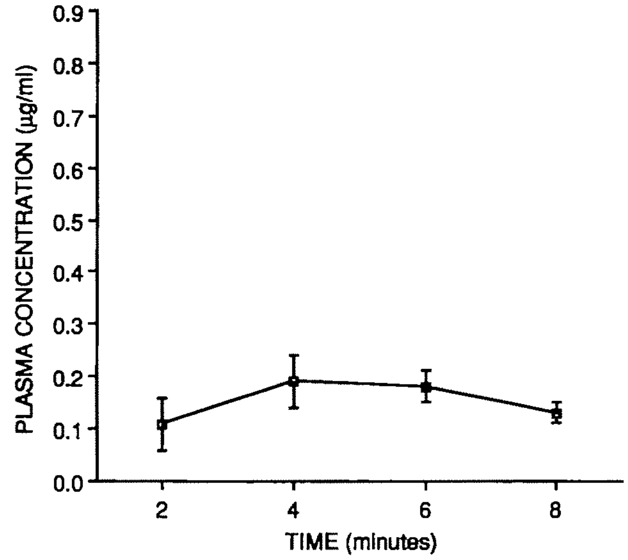

Figure 2. Infusion of vecuronium. Plasma concentration (mean ± SD µg/mL) of vecuronium as a function of time in minutes following the IV infusion of 0.015 mg/kg over 5 min.

plasma vecuronium levels in four patients receiving rapid bolus injection and at 2-min intervals in four patients receiving the slow infusion of vecuronium. The samples were analyzed at Gronigen University using a standard flurometric technique (2).

This study was approved by the Westminster Hospital Ethical Committee, and informed consent was obtained. Wilcoxon ranked paired *t*-test was the statistical method used.

Results

The plasma levels of vecuronium in the two groups of patients are shown in Figures 1 and 2. The large standard deviation of the peak plasma levels seen 60 sec after rapid injection reflects the well-documented difficulty of measuring blood concentration of a drug when it is changing rapidly (3). Because of this, the peak plasma level of vecuronium recorded must be less than that actually reached in these patients. At the end of 4 min the mean plasma levels in both groups of patients were approximately 2.25 µg/mL, whereas in the bolus injection group the mean peak plasma level at 1 min was 5.8 µg/mL.

The times to onset of maximum T_1 depression in the two groups of patients were significantly different (Table 1): in the bolus group 368 ± 84 (SD) sec and in the infusion group 615 ± 88 sec, a statistically significant difference.

Despite the different peak plasma concentrations, the mean of the depression of T_1 achieved in both the bolus and the infusion group was identical at 31% of the control (bolus 31 ± 22, infusion 31 ± 23). The maximum depression of T_4 in both groups was also identical (68 ± 15% in the bolus group 68 ± 20% in the infusion group). There was no significant difference in the T_4:T_1 ratio between the two groups.

It can be seen from Table 1 that although there is scatter in the mean figures for the amount of block within each group, if one studies each pair of patients there is generally a good correlation. As the vecuronium was made up anew for each pair, any minor discrepancy in dissolving and diluting the powdered drug would be reflected in differences between pairs rather than within pairs of patients. At the dose level of vecuronium used, very small variations in the log of the plasma concentration would result in large changes in receptor occupancy (4). When this is taken into account, the constancy of the results is good.

Discussion

In this study an ED_{50} dose, as determined by the difference between control and 100% block on an IEMG, was given either as a bolus or as an infusion. This resulted in a 2.5-fold difference in peak plasma concentration and a significant difference in the time to maximum blockade. There was no difference in the degree of blockade as assessed by either the percentage reduction in T_1 or the T_1:T_4 ratio as measured by IEMG.

It has been suggested that low cardiac output states might influence the rate of uptake of intravenously administered drugs (5,6). In this study this

Table 1. Times to Onset of Maximum Block in Patients Given Vecuronium by Bolus and by Infusion

Bolus						Infusion					
Pair	Weight (kg)	% Change T_1	% Change T_4	T_4:T_1 ratio	Time to maximum block	Pair	Weight (kg)	% Change T_1	% Change T_4	T_4:T_1 ratio	Time to maximum block
1	52	5	34	0.69	313	1	58	5	35	0.68	708
2	56	16	78	0.26	270	2	70	13	43	0.65	628
3	58	23	63	0.48	450	3	62	13	36	0.73	694
4	68	62	89	0.28	345	4	58	71	87	0.44	498
5	70	28	82	0.25	342	5	61	25	72	0.37	760
6	60	3	51	0.50	424	6	74	35	80	0.30	575
7	50	73	80	0.74	295	7	60	20	70	0.38	671
8	56	15	57	0.50	442	8	55	21	59	0.51	514
9	64	28	64	0.50	540	9	68	8	66	0.36	678
10	66	32	72	0.41	340	10	56	17	67	0.39	570
11	48	55	70	0.66	290	11	—	65	93	0.20	585
12	56	21	60	0.51	457	12	—	64	94	0.16	655
13	88	45	80	0.36	280	13	78	46	89	0.20	470

In each pair one patient was given 0.015 mg/kg vecuronium by bolus, the other by infusion. The percentage change in T_1, T_4, and the T_1:T_4 ratio is recorded, as is the time in seconds to maximum block. Wilcoxon rank paired *t*-test was used to compare the two groups. T_1, $P = 0.97$; T_4, $P = 1.0$; T_1:T_4 ratio, $P = 0.43$; time to maximum depression, $P = 0.0002$.

condition was simulated by an infusion of vecuronium. As anticipated, this produced a lower plasma level compared to rapid bolus injection (7), but no difference was demonstrated in the degree of neuromuscular block produced. This suggests that the peak plasma levels correlate poorly with clinical effect, as has been reported previously (5,8). The failure of the neuromuscular block to reflect the peak plasma levels indicates a slow equilibration between the plasma and the receptor. This is consistent with the presence of a "biophase" described in pharmacokinetic models (5,8,9) but not previously demonstrated clinically.

In this study the plasma levels in the bolus group at 3 to 4 min were similar to those in the infusion group. This may indicate the "biophase transit time," which includes the time for diffusion from the blood into the synaptic cleft and the time for receptor occlusion. If truly rapid-onset nondepolarising neuromuscular blocking agents are to be developed, this biophase delay must be overcome.

References

1. Schwarz S, Ilias W, Lackner F, Mayrofer O, Foldes FF. Rapid tracheal intubation with vecuronium: The priming principle. Anesthesiology 1985;62:388–91.
2. Kersten VW, Meijer DKF, Agoston S. Fluorimetric and chromatographic determination of pancuronium bromide and its metabolites in biological materials. Clin Chim Acta 1973;44:59.
3. Hull CS, Van Beem HBH, McLeod K. Sibbald A, Watson MJ. A pharmacodynamic model for pancuronium. Br J Anaesth 1978; 50:1113–23.
4. Paton WDM, Waud DR. The margin of safety of neuromuscular transmission. J Physiol (Lond) 1967;191:59.
5. Sheiner LB, Stanski DR, Vozeh S, Miller RD. Simultaneous modelling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. Clin Pharmacol Ther 1979;25:358–71.
6. Donati F, Bevan DR. The influence of patients' sex, age and weight on pancuronium onset time. Can Anaesth Soc J 1987;34: 555–9.
7. Stanski DR, Watkins WD. Drug Disposition in Anaesthesia. Grune and Stratton: New York, 1982:98.
8. Hull CJ, English MGM, Sibbald A. Fazadinium and pancuronium: A pharmacodynamic study. Br J Anaesth 1980;52:1209–20.
9. Donati F. Onset of action of relaxants. Can J Anaesth 1988;35;3: S52–S58.

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1989;69:627–32

A Comparative Study of Methods of Detection of Esophageal Intubation

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SUM-PING ST, MEHTA MP, ANDERTON JM. A comparative study of methods of detection of esophageal intubation. Anesth Analg 1989;69:627–32.

The trachea and esophagus of 21 patients were simultaneously intubated to comparatively evaluate methods for detecting esophageal intubation. In succession, the trachea and esophagus were ventilated with the same inspiratory volume of 621 ± 45 mL (mean ± SD). Carbon dioxide (CO_2) levels, volumes, and temperatures of expired gas were measured from the tracheal and esophageal tubes. End-expired CO_2 levels of gases from the trachea and esophagus were 4.9 ± 0.7% and 0.6 ± 0.6%, respectively, with CO_2 waveforms observed in 7 (33%) patients with esophageal intubations. Volumes expired from the tracheal tube averaged 615 ± 64 mL and from the esophageal tube 35 ± 16 mL ($P < 0.001$). Peak temperatures of expired gas recorded from the tracheal tube (32.0 ± 0.73°C) were higher than those from the esophageal tube (27.3 ± 1.2°C) ($P < 0.001$). The shape of temperature waveforms with a correctly placed tracheal tube remained constant with each ventilation, contrary to that obtained from an esophageal tube. Although the occasional detection of CO_2 waveforms from an esophageal tube might lead to an incorrect assessment of tube placement, this limitation of CO_2 analyzer can be offset by measurement of volume and temperature of expired gas in identifying placement of an endotracheal tube.

Key Words: INTUBATION, TRACHEAL.

Tracheal intubation is routinely performed to maintain and protect the airway during anesthesia or cardiopulmonary resuscitation. A major concern is the occasional failure to identify an esophageal intubation, a failure that may lead to irreversible brain damage or death (1–5). Of the available methods to identify correct placement of the tracheal tube, measurement of end-expired carbon dioxide (CO_2) is the most reliable, popular, and convenient (6). However, Linko et al. (7) observed end-expired CO_2 levels as high as 4.9% with an esophageal intubation when expired gas was deliberately introduced into the esophagus to simulate conditions during difficult ventilation with use of a face mask. In a recent case report (8), apparently normal appearing CO_2 waveforms were observed after an esophageal intubation. These reports suggest that if enough alveolar gas is inadvertently introduced into the esophagus/stomach during ventilation by face mask, normal appearing CO_2 waveforms can be observed during esophageal ventilation. Also, during cardiopulmonary resuscitation, when blood flow to the lungs may be poor, there may be little CO_2 delivery and, hence, a false impression of esophageal intubation if the CO_2 analyzer is relied on exclusively. Because of this limitation of the CO_2 analyzer in identifying the correct placement of the endotracheal tube, new methods are needed to improve or complement the CO_2 analyzer for the detection of esophageal intubation. One approach is to measure expired gas variables, including volume and temperature, to determine whether they can be used to distinguish between tracheal and esophageal intubation.

The aim of this study was to investigate whether measurement of volume and temperature of expired gas would complement CO_2 waveforms in assessing the correct placement of tracheal tubes.

Methods

Twenty-one ASA physical status I and II patients without history of esophageal or gastric pathology were studied after securing informed written consent and approval by the University Human Research

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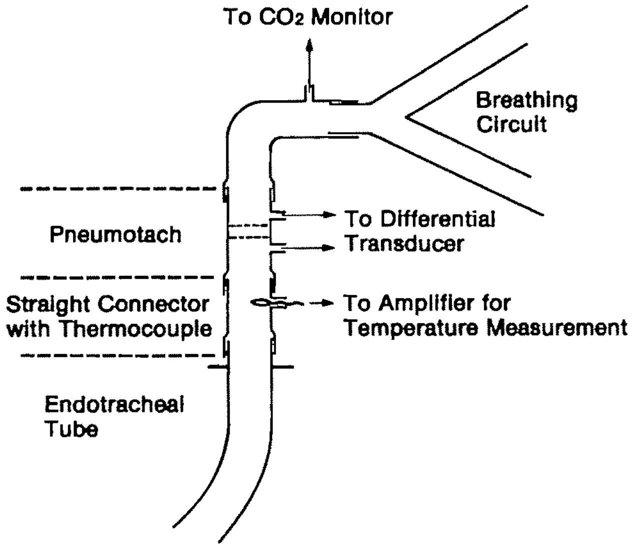
To CO2 Monitor
Breathing Circuit
Pneumotach
To Differential Transducer
Straight Connector with Thermocouple
To Amplifier for Temperature Measurement
Endotracheal Tube

Figure 1. A diagramatic representation of the measuring equipment attached between the endotracheal tube and the breathing circuit.

Review Committee. Patients with abnormal upper airway anatomy or those suspected of having difficult airways were excluded from the study.

All patients arrived in the operating room unpremedicated. After placement of intravenous cannula, electrocardiographic (ECG) electrodes, blood pressure cuff, and pulse oximetry probe, anesthesia was induced with fentanyl 3.0 μg/kg and sodium thiopental 4–5 mg/kg IV. The patient's lungs were hand-ventilated with use of a face mask with tidal volume of approximately 500–600 mL of 1–2% isoflurane in oxygen 10 times per minute. After ascertaining that the airway was patent, patients were paralyzed with either vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg. Three minutes after the administration of muscle relaxant, the trachea and esophagus were simultaneously intubated with 7.5-mm endotracheal cuffed tubes and the cuffs inflated with up to 10 mL air. The tracheal tube was attached to a mechanical ventilator set to deliver a tidal volume of 8 mL/kg 10 times per minute. Anesthesia was maintained with 1–2% isoflurane in oxygen.

Once a steady state of anesthesia was achieved, equipment consisting of a port for measuring level of CO_2 (Beckman LB II), a Fleisch pneumotachograph, and a thermocouple were placed between the tracheal tube and the Y connector of the circle system (Figure 1 and Appendix). After recording data during three ventilations of the lungs (total duration = 18 sec), the circle system with measuring equipment was switched to the esophageal tube and three further "ventilations," with the setting on the ventilator unchanged, were administered. The fresh gas flow was set at 8 L/min during the experiment to assure that the bellows of the ventilator were fully inflated after each esophageal "ventilation." After esophageal "ventilation," the circle system and measuring equipment were switched back to the tracheal tube for normal lung ventilation, and the patient's stomach was deflated with an oral gastric tube passed through the esophageal tube. To simulate an incompetent gastroesophageal sphincter, the gastric tube was cut at the level of the connector of the esophageal endotracheal tube in 13 patients, and three further "ventilations" were again administered with the circle system and measuring equipment connected to the esophageal tube with the cut gastric tube in situ. Anesthesia was continued after measuring equipment and esophageal tube were removed. The oral gastric tube was removed after the stomach was deflated.

During ventilation of the tracheal and esophageal tubes, CO_2 and temperature of expired gas were recorded with linear penwriter and data obtained from volumes exhaled were digitized and stored on floppy disk with use of an IBM personal computer.

Statistical analysis was performed with paired *t*-test. $P < 0.05$ was considered statistically significant. The results are given as mean ± SD.

Results

Ventilation with face mask was easily maintained in all patients and peak inspiratory pressure did not exceed 25 cm H_2O to maintain adequate ventilation as measured by end-expired CO_2. The volumes exhaled and the temperatures and CO_2 waveforms of expired gas were easily recorded from both the tracheal and esophageal tubes. A good cuff "seal" was difficult to achieve with esophageal intubation and leaks were still present even when volumes as large as 10 mL were introduced into the cuff. The duration of the experiment was approximately 3 min; arterial oxygen saturation never decreased below 98% in any patient.

The end-expired CO_2 of gas from the trachea averaged 4.9 ± 0.7%. In 7 (33%) patients, CO_2 waveforms were recorded from the esophageal tube. The shape of CO_2 waveform obtained with esophageal intubation was similar to that obtained with tracheal intubation, but the mean level was significantly lower at 0.6 ± 0.6% ($P < 0.001$). The highest expired CO_2 level recorded from the esophageal tube was 2.0% (second "ventilation" in case No. 17). The first and third "ventilation" in the same patient had a CO_2 level of 1.6% and 1.8%, respectively (Figure 2). The end-expired CO_2 level from the tracheal tube in the same patient was 5.2%.

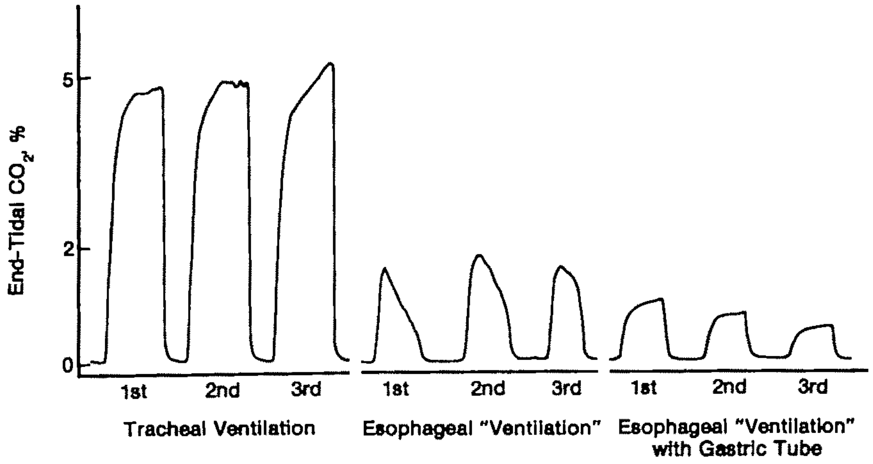

Figure 2. CO_2 waveforms of expired gas with tracheal and esophageal ventilation in case No. 17. Note that the rate of decrease in CO_2 level from the esophageal tube, before insertion of the gastric tube, does not follow the normal washout pattern.

Table 1. Peak Expiratory Temperatures and Volumes Recorded with Tracheal and Esophageal Ventilation (Mean ± SD)

	Tracheal ventilation			Esophageal ventilation (EV)			EV with gastric tube		
Breaths	1	2	3	1	2	3	1	2	3
n	13	13	13	13	13	13	13	13	13
Volume expired (mL)	621 ± 45	630 ± 44	629 ± 43	35 ± 16*	44 ± 21*	46 ± 17*	138 ± 37*	158 ± 31*	159 ± 29*
n	21	21	21	21	21	21	14	14	14
Peak temp (°C)	32.0 ± 0.73	32.3 ± 0.82	32.3 ± 0.82	27.3 ± 1.20†	27.3 ± 1.30†	27.6 ± 1.35†	27.5 ± 1.00†	27.4 ± 1.00†	27.4 ± 1.00†

*$P < 0.001$ inspired vs expired. †$P < 0.001$ esophageal vs tracheal.

The tidal volume delivered by the ventilator averaged 615 ± 64 mL. The exhaled volumes of gas from the correctly placed endotracheal tube averaged 621 ± 45 mL with the first ventilation and did not change significantly with the second or third ventilation (Table 1). The volumes of exhaled gas from the esophageal tube, with a range of 15–80 mL, were significantly less than the volumes delivered by the ventilator ($P < 0.001$). With simulation of an incompetent gastroesophageal valve, the volumes exhaled, ranging from 96 to 225 mL, were also significantly smaller than those delivered by the ventilator ($P < 0.001$). The leaks that occurred during esophageal "ventilation" were not measured.

A typical temperature waveform during ventilation of the lung and esophagus is shown in Figure 3. The temperature waveforms obtained during each ventilation of the tracheal tube had the same peak and shape and were identical to each other, whereas those obtained from the esophagus had different peaks and varied from each "ventilation" to "ventilation." With a simulated incompetent gastroesophageal sphincter, the shape of temperature waveforms obtained from the esophageal tube changed to a square wave (Figure 3). Peak temperatures recorded from the trachea were higher than those recorded from the esophagus in all instances (Figure 4). There was also a significant difference between the mean of peak temperatures recorded from the trachea and that from the esophagus ($P < 0.001$) (Table 1). The pattern of temperature difference recorded from the trachea and esophagus was unchanged with simulation of an incompetent gastroesophageal sphincter. The lowest temperature recorded from a tracheal tube was 30.8°C, whereas the highest temperature recorded from an esophageal tube was 29.7°C. With a simulated incompetent gastroesophageal sphincter, the highest temperature recorded from the esophageal tube was 29.2°C.

Discussion

The degree of reliance on any monitor to identify correct placement of a tracheal tube depends on the frequency of false positives and false negatives. One assumes correct placement of a tracheal tube with the observance of expired CO_2 waveforms because CO_2 is excreted only from the lung. But it is possible to obtain a similar waveform from the esophagus when

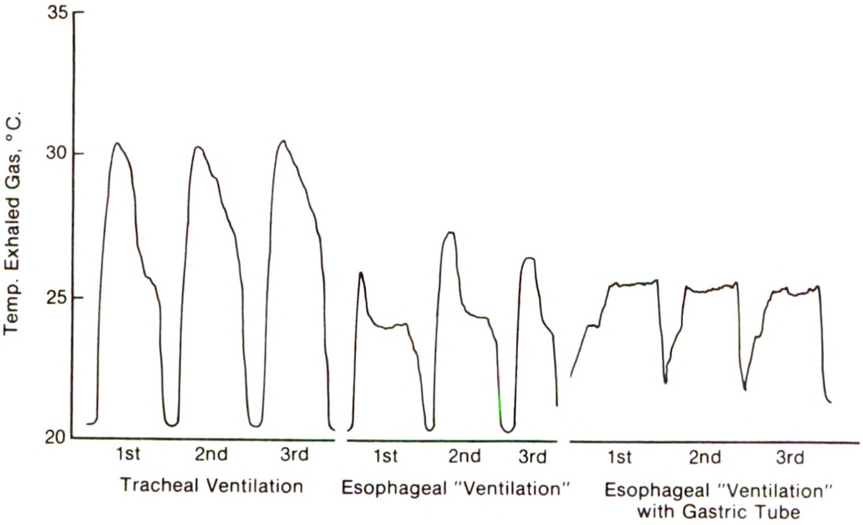

Figure 3. Temperature waveforms of expired gas with tracheal and esophageal ventilation. Note the different shapes and peaks between the waveforms of gas expired from the trachea and esophagus (in the presence and absence of a gastric tube).

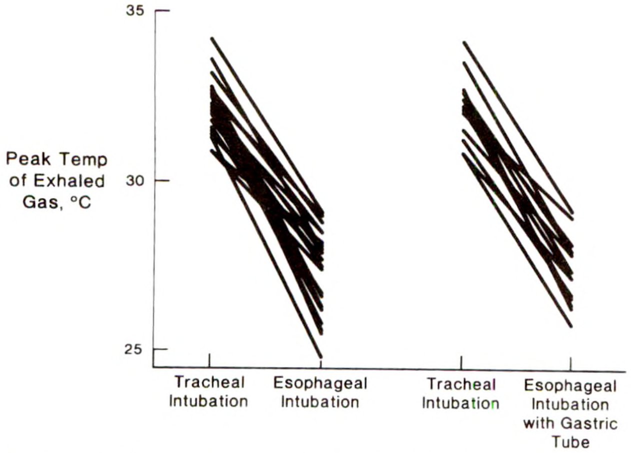

Figure 4. Peak temperatures of expired gas recorded with "first ventilation" of the tracheal and esophageal tubes.

enough alveolar gas is forced down the esophagus/stomach during ventilation by face mask (especially in patients with a difficult airway) (7–9). False negatives may occur during cardiopulmonary resuscitation when low cardiac output increases physiological dead space with a low end-expired CO_2. The cardiac output, at times, may be so low as to make the CO_2 waveforms nearly nonexistent.

Linko et al. (7) found that a CO_2 waveform was obtained in 9 of 20 (45%) esophageal intubations, albeit at low concentrations (0.2–1.5%). In the present study, although every patient studied had a clear airway during induction of anesthesia, subsequent expiratory CO_2 waveforms were obtained in 7 (33%) cases of esophageal intubations, the highest CO_2 level being 2%. The pattern of decrease in CO_2 level associated with esophageal ventilation has been suggested as resembling a conventional washout curve (10). But the normal exponential washout pattern would certainly not be expected in the presence of esophageal intubation because the CO_2 washout curve with esophageal ventilation will vary according to the amount of gas entering and leaving the esophagus/stomach. The volume of intraesophageal or intragastric gas movement would depend on the distensibility of the esophagus (resulting in leaks around the cuff), tone of gastroesophageal sphincter, and intragastric pressure. During esophageal intubation, the CO_2 level with each expired volume, in addition, will depend on the degree of mixing that occurs as gas from the stomach enters the esophagus. This is supported by the constant pattern of CO_2 waveforms observed in one case report (8) and case No. 17 in the present study. Good et al. (11) concluded that the CO_2 waveform obtained from the esophageal tube is different from that of the tracheal tube after three "ventilations." Their study was done by ventilating the stomach of a dog through a gastrostomy and with a tube in the esophagus of a mechanical stomach model; therefore, it is difficult to extrapolate their data and results to humans.

The volumes expired from the esophagus in the present study were smaller than those inspired, whereas there was no significant difference between inspired and expired volumes during tracheal ventilation. Lack of an efficient recoil mechanism in esophagus/stomach, gas trapping in stomach, and leaks around the cuff explain the decrease in expired volume with esophageal ventilation. The magnitude by which expired volume decreased with esophageal ventilation was an important finding that would not be affected in situations of low CO_2 excretion. Measurement of volume of expired gas appears to be at least as reliable as, if not better than, data obtained by measuring CO_2 levels for determining placement of a tracheal tube.

Measurement of volumes expired were made with a pneumotachograph instead of a respirometer. The pneumotachograph, with the advantage of being bidirectional and having a rapid response time, provided the capability of comparing inspired and expired volumes instantaneously. In addition, its small size allowed it to be attached between the endotracheal tube and the Y connector, hence, eliminating errors in circuit compliance. The disadvantage of nonlinear flows with the pneumotachograph can be avoided by choosing the correct size. With advances in electronics, the pneumotachograph is easy to use and, we believe, should be considered as an integral part of the anesthetic machine.

The accuracy of temperature measurements of gases depends on the specific heat capacity of the thermocouple used. The lower temperature recorded from the esophageal tube in the present study was due either to a genuine lower temperature or because the volume of gas exhaled was too small to achieve equilibration of temperature with the thermocouple for accurate measurement. With simulation of an incompetent gastroesophageal sphincter, the volume exhaled from the esophageal tube was over the critical amount for accurate recording of temperature (see Appendix). Nevertheless, the peak temperatures obtained before insertion of the gastric tube were similar to those obtained with simulation of an incompetent gastroesophageal sphincter, probably because the humidity present in the exhaled gas reduces the critical volume necessary for the accurate reading of temperature.

The peak and shape of the temperature waveform depend on the temperature and flow of the gas exhaled, respectively. During exhalation of gas, the temperature increased to a peak as soon as enough alveolar gas was flowing past the thermocouple; as flow of gas decreased during expiration, the temperature recorded decreased at a similar rate to give a waveform that was similar to an expiratory flow curve. Therefore, temperature waveforms obtained from tracheal tubes were similar in shape and peak with each ventilation. In contrast, the temperature waveform was dissimilar with each esophageal ventilation, resulting from the erratic flow, as explained in the preceding paragraph. With a simulated incompetent gastroesophageal sphincter, the temperature waveforms were square-shaped, probably due to a constant flow of gas from the stomach through the gastric tube during "expiration." The peak temperature of expired gas suffers the same limitation as the end-expired CO_2 level because the amount of heat excreted through the lung with each ventilation depends on the blood flow to the lung and ventilation/perfusion matching. This and the heat lost through the portion of endotracheal tube lying outside the mouth explain the low temperature of expired gas from the lung. The peak temperature of expired gas before induction of anesthesia, if known, could provide a target temperature.

Humidity is commonly mentioned as an indicator of a correctly placed endotracheal tube. In this study, humidity was not measured because its reliability for detecting esophageal intubation has already been investigated (12). Gillespie et al. (12) found condensation in the esophageal tube in 28.6% of patients with an esophageal intubation and concluded that humidity should not be used as a reliable indicator of proper intubation.

When the vocal cords have not been visualized during laryngoscopy and intubation, one should probably not rely on one monitor but rather on two or three independent monitors to confirm proper placement of an endotracheal tube. Though the CO_2 analysis is usually accurate in identifying correct placement of a tracheal tube, the occasional detection of CO_2 waveforms with esophageal intubation and the low levels or absence of CO_2 with tracheal intubation during cardiopulmonary resuscitation might lead to an incorrect assessment. The limitation of measurement of expired CO_2 for identifying esophageal intubation can be offset by measurement of volume and temperature of expired gas. Measurement of expired volume with a pneumotachograph may be an important improvement over CO_2 waveforms in assessing accuracy of placement of tracheal tubes.

We are indebted to Drs. Mohamed M. Ghoneim and John H. Tinker for reviewing the manuscript, Dr. Franklin L. Scamman for writing the computer program for data storage, and Ms. Heidi Butler for secretarial assistance.

Appendix

Omega Thermocouple

A copper-constantan thermocouple (size 0.002 in., Omega Co.) was used in this study. It was tested in our laboratory for accuracy and for determining whether its specific heat capacity was appropriate for measuring small volumes of air.

The accuracy of the thermocouple was determined by comparing it with a mercury thermometer certified by the National Bureau of Standards. The thermocouple and mercury thermometer were placed close to each other in a beaker of water with a stirrer at the bottom. The water was slowly heated and temperature recorded from the thermocouple and mercury thermometer simultaneously. The relationship was found to be linear with regression value of 0.999 and slope of 1.0037.

The relative specific heat capacity of the thermocouple was determined by blowing across the thermocouple an increasing volume of ambient air at 37°C over a 2 sec period (duration of expiratory phase). When the volume of air was below 90 mL, the temperature recorded by the thermocouple increased in proportion to the increase in volume. At a volume of 90 mL and above, the temperature recorded remained steady at 37°C. This meant that 90 mL was the minimal volume of air required for the thermocouple to record temperature accurately.

Fleisch Pneumotachograph

Fleisch pneumotachograph, size No. 0, was chosen because it provides good accuracy of flow up to 15 L/min. A bigger size would have provided better accuracy during the initial part of expiration but would not be sensitive enough for the low flow from the esophagus. The pneumotachograph was calibrated with a super syringe before each experiment.

References

1. Peterson AW, Jacker LM. Death following inadvertent esophageal intubation: a case report. Anesth Analg 1973;53:398–401.
2. Utting JE, Gray TC, Shelley FC. Human misadventure in anaesthesia. Can Anaesth Soc J 1979;26:472–8.
3. Lunn JN, Hunter AR, Scott DB. Anaesthesia-related surgical mortality. Anaesthesia 1983;38:1090–6.
4. Hunter AR. Towards safer anaesthesia in obstetrics. Br J Anaesth 1987;59:275–6.
5. Keenan RL, Boyan CP. Cardiac arrest due to anesthesia: a study of incidence and causes. JAMA 1985;253:2373–7.
6. Birmingham PK, Cheney FW, Ward RJ. Esophageal intubation: a review of detection techniques. Anesth Analg 1986;65:886–91.
7. Linko K, Paloheimo M, Tammisto T. Capnography for detection of accidental oesophageal intubation. Acta Anaesthesiol Scand 1983;27:199–202.
8. Sum-Ping ST. Esophageal intubation (letter). Anesth Analg 1987.66:483.
9. Sum-Ping ST. Esophageal intubation (letter). Anesth Analg 1988;67:195–6.
10. Salzarulo HH, Leiman BC, Katz J, Butler B. Carbon dioxide detection and esophageal intubation (letter). Anesth Analg 1988;67:195.
11. Good ML, Modell JH, Rush W. Differentiating esophageal from tracheal capnograms. Anesthesiology 1988;69:A266.
12. Gillespie JH, Knight RG, Middaugh RE, Menk EJ, Baysinger CL. Efficacy of endotracheal tube cuff palpation humidity in distinguishing endotracheal from esophageal intubation. Anesthesiology 1988;69:A265.

Special Article

A Cardiogenic Hypertensive Chemoreflex

Thomas N. James, MD, MACP

JAMES TN. A cardiogenic hypertensive chemoreflex. Anesth Analg 1989;69:633–46.

A cardiogenic hypertensive chemoreflex is elicited by serotonin administered experimentally in the dog. The reflex nearly doubles aortic pressure within 4–6 sec and is associated with powerful inotropic, chronotropic, and dromotropic responses. The afferent pathway is via intrathoracic vagal branches, whereas the efferent paths engage not only the vagal and sympathetic routes but also the phrenic nerve. The reflex can be abolished by vagotomy or with cyproheptadine, and can be attenuated by local anesthesia of the intertruncal space. Small chemoreceptors lying between the aorta and pulmonary artery are the source of the reflex, and they receive their blood supply from the proximal left coronary artery. Human counterparts of the reflex may include new hypertension during angina pectoris or acute myocardial infarction, new postoperative hypertension after coronary bypass grafting, and hypertensive patients with carcinoid syndrome. Many unresolved problems include the precise mechanism of chemoreception, whether the chemoreflex has any tonic influence, and mechanisms of integration of the reflex with other events peripherally and centrally. Answers to these questions could be of great clinical value.

Key Words: BLOOD PRESSURE, HYPERTENSION—cardiogenic. SEROTONIN, CARDIOGENIC HYPERTENSION. REFLEXES, CHEMORECEPTORS—cardiac. HEART, CHEMOREFLEXES.

Most reflex events significantly influence the performance of the heart, but it is not as widely appreciated that the heart itself can be the source of important reflexes. The two general categories of cardiogenic reflexes include those responding to changes in pressure (baroreflexes, pressoreflexes, spatial deformation reflexes) and those responding to chemical stimuli (chemoreflexes). In addition to the more familiar baroreflexes such as those originating because of changes in pressure within a cardiac chamber or a coronary artery, there are other more subtle and complex but equally important cardiogenic baroreflexes, such as the one that is inducible experimentally in the dog to generate flow within an adrenorenal rete, causing blood with a high concentration o catecholamines to flow directly from the adrena medulla to the renal cortex (1,2).

Chemoreflexes from the heart have been mos extensively studied with topical application or direc injection of certain toxic alkaloids, e.g., nicotine, lobeline, or capsaicin; less is known about the role o natural body substances in the production of such reflexes. Furthermore, there is a regrettable tendency to think of chemoreflexes as being caused exclusively by changes in pH, oxygen tension, or carbon dioxide concentration. Whereas this misconception is understandable (given the importance of the blood gas monitoring function of structures such as the carotid body), the restrictive nature of that interpretation is particularly illustrated by the cardiogenic hypertensive chemoreflex.

In 1939 Julius Comroe determined that a hypertensive chemoreflex could be elicited in dogs and cats from receptors located very near the main left coronary artery and that the blood supply for those receptors often originated from a coronary artery (3)

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In 1965 Horwitz and Sjoerdsma (4) studied four patients suspected of having pheochromocytoma because of severe paroxysmal hypertension; instead of pheochromocytoma they found that the hypertensive episodes closely related to bouts of angina pectoris, from which they deduced that the source must be a chemoreceptor within the heart. In 1966 Becker searched for Krahl's pulmonary glomus; he failed to find it but he did describe two sets of intertruncal glomera lying between the pulmonary artery and ascending aorta, with the lower set receiving its blood supply from the proximal left coronary artery (5). In 1971 Eckstein and his colleagues studied a cardiogenic hypertensive chemoreflex in dogs and made two especially important contributions: that the chemoreflex could be elicited by 5-hydroxytryptamine (which occurs normally in the blood of humans and most other mammals), and that the blood supply to the responsible chemoreceptor came from either the main left coronary artery or proximal few millimeters of its two branches in virtually all of the dogs (6).

Since 1975 my colleagues and I have investigated the multiple facets of this cardiogenic hypertensive chemoreflex (7), including its neural pathways and the pharmacologic blockade of the reflex with some but not all serotonin antagonists (8), changes in regional flow patterns during the reflex (9), the several different hemodynamic components of the reflex (10), behavior of the chemoreflex in the awake state and especially in relation to breathing (11), the interplay between this chemoreflex and certain baroreflexes (12), possible role of the chemoreflex in the new hypertension occurring during acute myocardial infarction (13) or in the postoperative period after coronary artery bypass grafting (14), fine structure of the coronary chemoreceptor (15), and pathologic changes found within and near the coronary chemoreceptor in victims of sudden unexpected death (16).

In many respects the cardiogenic hypertensive chemoreflex is the mirror image of the Bezold–Jarisch reflex, which has been known for over a century (17) but has also received more recent attention (18–20). Both reflexes, interestingly, can be produced by serotonin (5-hydroxytryptamine), although the sites of chemoreception differ (Figure 1). Also, both reflexes can be blocked with discrete local anesthesia of the intertruncal space, which is discussed later. Furthermore, both the Bezold–Jarisch reflex and the cardiogenic hypertensive chemoreflex are significantly related to the clinical picture associated with acute myocardial infarction (21–23).

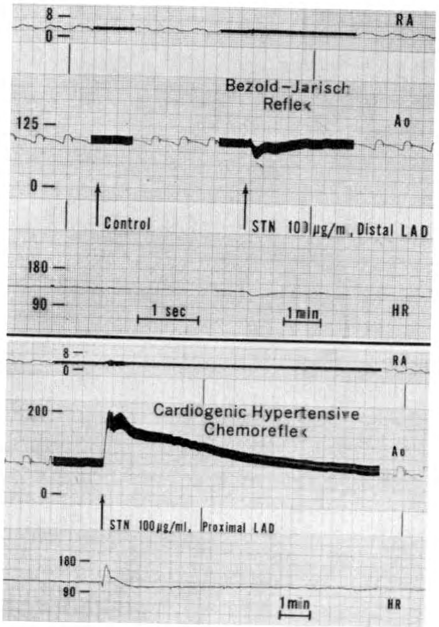

Figure 1. This experiment illustrates the contrasting effect of serotonin (STN) when injected into the distal left anterior descending coronary artery (LAD) or into a small proximal branch of the LAD of the same dog. The Bezold–Jarisch response causes hypotension and bradycardia, while the cardiogenic hypertensive chemoreflex causes hypertension and tachycardia. The control injection is diluent, which was Ringer's solution. The two upper tracings are pressure recordings from the right atrium (RA) and aorta (Ao), scaled in mm Hg, and the lower trace is a tachogram, scaled in beats/min. Recording paper speed is indicated with a reference bar. (With permission from ref. 7.)

Functional Components of the Cardiogenic Hypertensive Chemoreflex

Relatively small amounts of serotonin injected into the nutrient artery of the coronary chemoreceptor (6,7) or into the left atrium of the dog (7) cause an abrupt hypertension virtually doubling systemic arterial pressure within 4–6 sec (Figure 1). Comparable injections of serotonin into the ascending aorta or the carotid arteries do not cause this response. There is no tachyphylaxis in the hypertensive response to serotonin (7,10). The afferent pathway for this reflex courses within one or more intrathoracic vagal branches (8), but the efferent response engages not only the vagal and sympathetic systems but also the phrenic nerve (11). Cooling or sectioning the vagi eliminates the reflex (6,7), although a lesser degree of late onset hypertension can still be observed after left atrial injections of serotonin; this later hypertension is due to release of catecholamines from the adrenal medulla during circulation of the administered serotonin to the adrenal glands, and can be eliminated by interrupting the adrenal blood supply, by adrenalectomy, or by prior pharmacologic depletion of adrenal catecholamine stores (10).

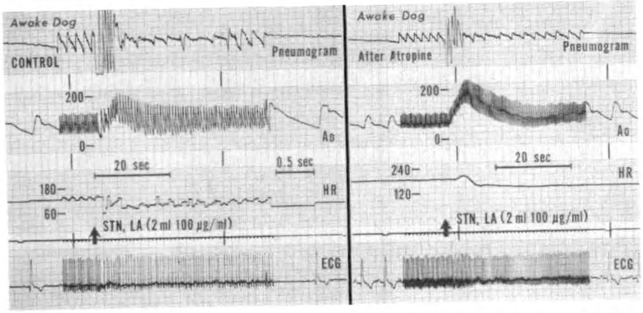

Figure 2. In the awake dog there is a highly variable vagal reflex component which may modify the hypertensive response to serotonin, here administered into the left atrium (LA), with results comparable to those from intracoronary injections. When the dog was treated with atropine 1 mg/kg IV, the vagal reflex was eliminated, and instead of bradycardia there was sinus tachycardia during the hypertension. Note that ventilatory effects, expressed by gasps visible in the pneumogram, have no significant influence upon the hemodynamic or electrophysiologic effects of the chemoreflex. (With permission from ref. 11.)

The hypertensive response differs in the awake dog only by the presence of a more profound component of the vagal efferent influence, causing either marked bradycardia or heart block; however, the intensity of this vagal response varies greatly from one dog to another. When the vagal response is eliminated by the administration of atropine, the hypertension in awake dogs (Figure 2) closely resembles that of anesthetized dogs. Ventilatory events (hyperpnea, gasping) last only a few seconds at the start of the reflex and do not themselves significantly influence the cardiogenic hypertensive chemoreflex (11).

At the onset of the cardiogenic hypertensive chemoreflex two effects combine to produce the marked hypertension: there is a prompt and powerful positive inotropic effect on ventricular myocardium (Figure 3), and at the same time there is marked vasoconstriction in major systemic vascular beds (9). Important exceptions to this immediate vasoconstriction include the coronary circulation, the carotids, and the pulmonary arteries; by contrast, the renal, mesenteric, and femoral arterial flows all sharply decrease (9). In the atria there is a mixed vagal and sympathetic effect during which the negative inotropic response predominates if atropine has not been administered, but there is a prominent positive inotropic atrial effect in the presence of atropine (Figure 4).

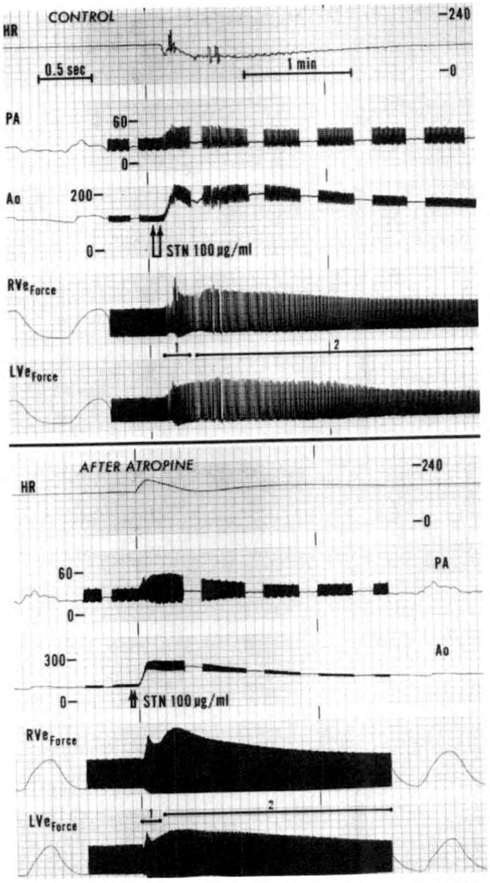

Figure 3. Force gauge recordings from the right (RVe) and left (LVe) ventricles demonstrate a biphasic positive inotropic response during the reflex when serotonin is administered into the left atrium. The first phase is numbered 1 and is purely a manifestation of the reflex; the second phase is numbered 2 and includes not only the reflex effect but also the influence of catecholamines released from the adrenal medulla directly by the serotonin, as discussed in the text. Atropine eliminates the bradycardia and permits only the positive chronotropic effect of the reflex. Note that pulse pressure widens in the pulmonary artery (PA) during the reflex, but there is only minimal influence upon mean pressure. (With permission from ref. 10.)

Chronotropic and dromotropic events during the cardiogenic hypertensive chemoreflex similarly demonstrate the coexistence of both vagal and sympathetic effects (Figure 5). By direct perfusion of 10 μg of atropine into the cannulated sinus node artery or atrioventricular (AV) node artery of the dog (24–26), one can selectively eliminate the local vagal influence, permitting separate examination of all electrophysiologic consequences of vagal influence *except* that affecting either the sinus node or the AV node (or both). For example, heart block occurs during the reflex when the sinus node response has been selectively eliminated (Figure 6), whereas selective elimination of sympathetic neural influence on the sinus node during the reflex (after 10 μg of propranolol into the sinus node artery) leads to the emergence of AV junctional tachycardia instead of sinus tachycardia, if atropine had been previously perfused into the AV node artery. These several experimental perturbations are described to illustrate useful methods for "dissecting" out the multiple concomitant components of the cardiogenic hypertensive chemoreflex.

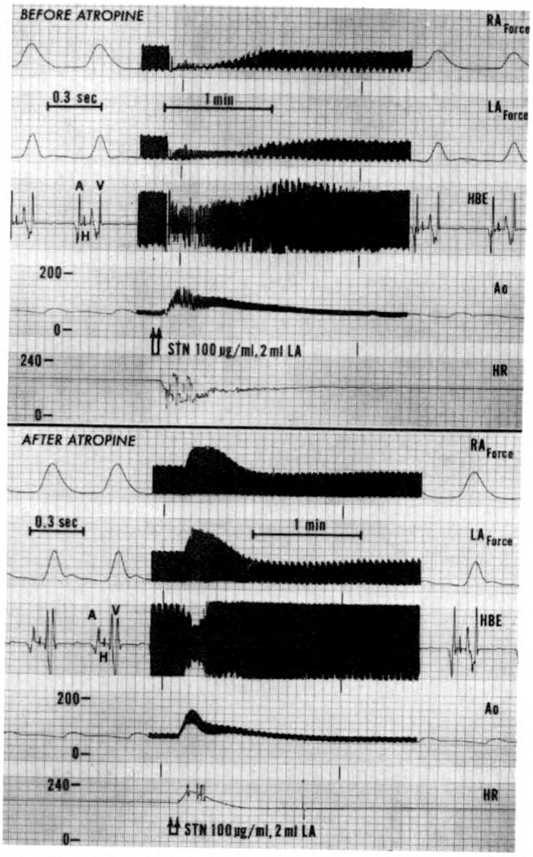

Figure 4. Before atropine the cardiogenic hypertensive chemoreflex causes only a negative inotropic effect upon the atria, but this is converted to a positive effect after atropine. Force gauge records from the right (RA) and left (LA) atria demonstrate a comparable effect on both atria. A bipolar recording from the His bundle (HBE) is included in this record, with atrial, ventricular and His bundle inflections marked A, H, and V. (With permission from ref. 10.)

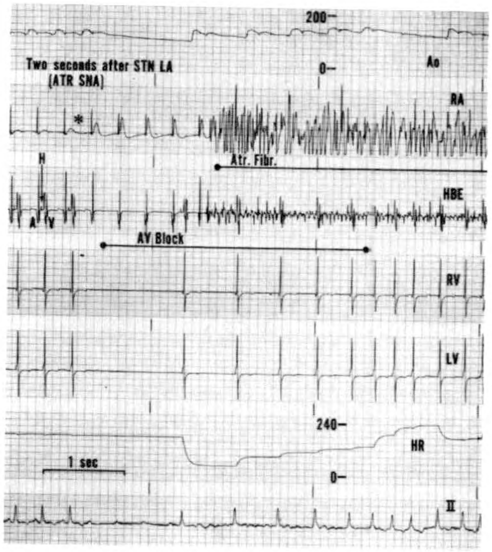

Figure 5. In this experiment 10 µg of atropine (ATR) was perfused into the sinus node artery (SNA) shortly before injecting serotonin 2 mL, 100 µg/mL, into the left atrium. Several elements of electrical "chaos" ensued as the chemoreflex began. Since the sinus node received atropine, sinus rate did not slow but because other components of the atria did not receive atropine, a distinct elevation of the atrial repolarization segment is seen in the right atrial electrogram (RA) just before the onset of atrial fibrillation. Both before the atrial fibrillation and for a few seconds afterward, there was a period of heart block visible, because no atropine was administered into the AV node artery. In addition to the RA and HBE electrograms, right ventricular and left ventricular electrograms were included here along with surface lead II. (With permission from ref. 7.)

Neurograms recorded during the reflex demonstrate that the entire efferent neural discharge lasts only a few seconds (Figure 7), although both the hemodynamic and electrophysiologic consequences continue for a longer time. As is often the case, afferent neurograms are difficult to obtain. A more convenient method for identifying the responsible afferent neural pathways is by selective cooling or sectioning of suspected nerves (8). From our few successful efforts to obtain afferent neurograms, we have determined that serotonin does produce impressive activity in the afferent nerve and that the activity is completely eliminated by the administraion of the serotonin blocking agent cyproheptadine but not by methysergide (8); however, this is a ompetitive blockade and can be overridden by the dministration of appropriately larger amounts of erotonin. There is remarkable symmetry in different omponents of the sympathetic neural efferent reponse (27), and a coexistent but slightly different iming and duration of the vagal efferent activity. The vagal difference is in part attributable to secondary activation of aortic and other baroreflexes by the reflex hypertension produced. There is a postexcitatory depression of neural activity immediately after the initial effective burst (28).

Evidence that the chemoreflex originates from receptors located within the intertruncal space includes the existence of chemoreceptor tissue there (discussed later), the production of the reflex by selective administration of serotonin into a small artery perfusing the intertruncal space (6,7), a lesser elicitation of the reflex by interstitial injection of serotonin into the intertruncal space (7), elimination of the reflex or marked obtunding of it by selective anesthesia produced by interstitial injection of lidocaine or another local anesthetic into the intertruncal space (7), and by recording of afferent neural traffic during the reflex from a small nerve leaving the intertruncal space (8).

Anatomical Substrate of the Cardiogenic Hypertensive Chemoreflex

Within the intertruncal space of human and canine hearts there is a plethora of neural structures includ-

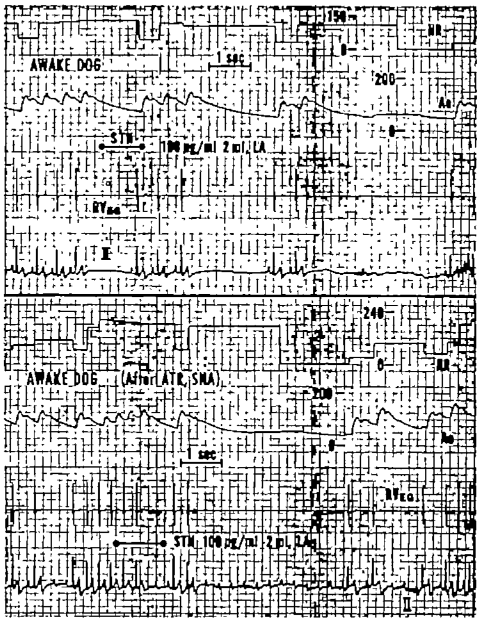

Figure 6. Reflex heart block (see also Figure 5) is distinctive in the awake dog, where resting vagal tone is normally higher. When the cardiogenic hypertensive chemoreflex was produced (upper record), the marked sinus arrhythmia (normally present) was accentuated during the reflex, and no escape rhythm emerged. After selective perfusion of the sinus node with atropine, the same reflex now was associated with complete heart block for a period during which sinus rhythm was not only unsuppressed but actually accelerated. In the tachogram (HR) which was set to read ventricular complexes, irregularity was apparent in both experiments. (With permission from ref. 98.)

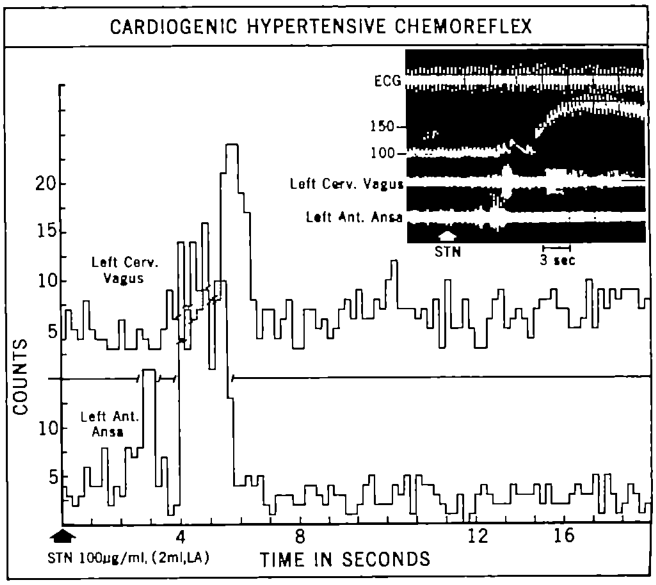

Figure 7. Both vagal (left cervical) and sympathetic (left anterior ansa) neurograms are illustrated during the cardiogenic hypertensive chemoreflex at the upper right. Computerized counts of signals from the neurograms are plotted below. Note the brevity of increased neural traffic and the secondary burst of activity in the vagal neurogram when the hypertension activates baroreceptors. (With permission from ref. 27.)

ing myelinated and unmyelinated nerves and numerous ganglia as well as multiple small grape-like clusters of glomoid tissue (Figures 8 and 9). Beginning near the origin of the aorta and pulmonary artery and continuing almost to the bifurcation of the latter there are several glomera, all of which resemble each other histologically. Furthermore, at the electron microscopic level they not only resemble each other but they are also indistinguishable from either the light or electron microscopic appearance of the carotid body. However, the fact that the cardiogenic hypertensive chemoreflex can be produced by activation of the coronary chemoreceptor with serotonin, whereas similar administration into the carotid circulation does not have this effect, leads one to suspect that there may be subtle but important differences even in the histologic organization, if suitably investigated with special methods.

As indicated by others (5,29), the blood supply to the upper group of glomera within the intertruncal space may come from the aorta, whereas that to the lower glomera (nearer the heart) is almost always derived from the proximal left coronary circulation (5–7). It seems reasonable, therefore, to refer to the latter group as coronary chemoreceptors rather than aortic bodies. In the normal human heart there are usually two to five small coronary chemoreceptors; some are "beaded" along one nutrient artery, whereas others have a distinctly separate blood supply, although those different arteries are usually the terminal branches of a single vessel coming from the left coronary artery. Some have described pressoreceptive vessels in the vicinity of these intertruncal glomera (5,30,31), and I have seen such vessels in human hearts.

Similar coronary chemoreceptors can be found in the intertruncal space of human, canine, and feline hearts (5–7,15). In both human and canine hearts the content of the coronary chemoreceptors includes many small nerves, arteries, arterioles and capillaries, and scattered mast cells. But their characteristic features are numerous clusters or "zellballen" of granulated cells (chief cells) interspersed with sustentacular cells (Figure 10). The chief cells are about twice as numerous as the sustentacular cells. Granules in the chief cells resemble those of similar cells in the carotid body and adrenal medulla, suggesting that those in the coronary chemoreceptor also produce and store amines. However, the fine structural features of the synapses between local nerves and the chief cells suggest that the chief cells in the coronary chemoreceptors may not only store amines but also serve as sensory or chemoreceptive sites (15).

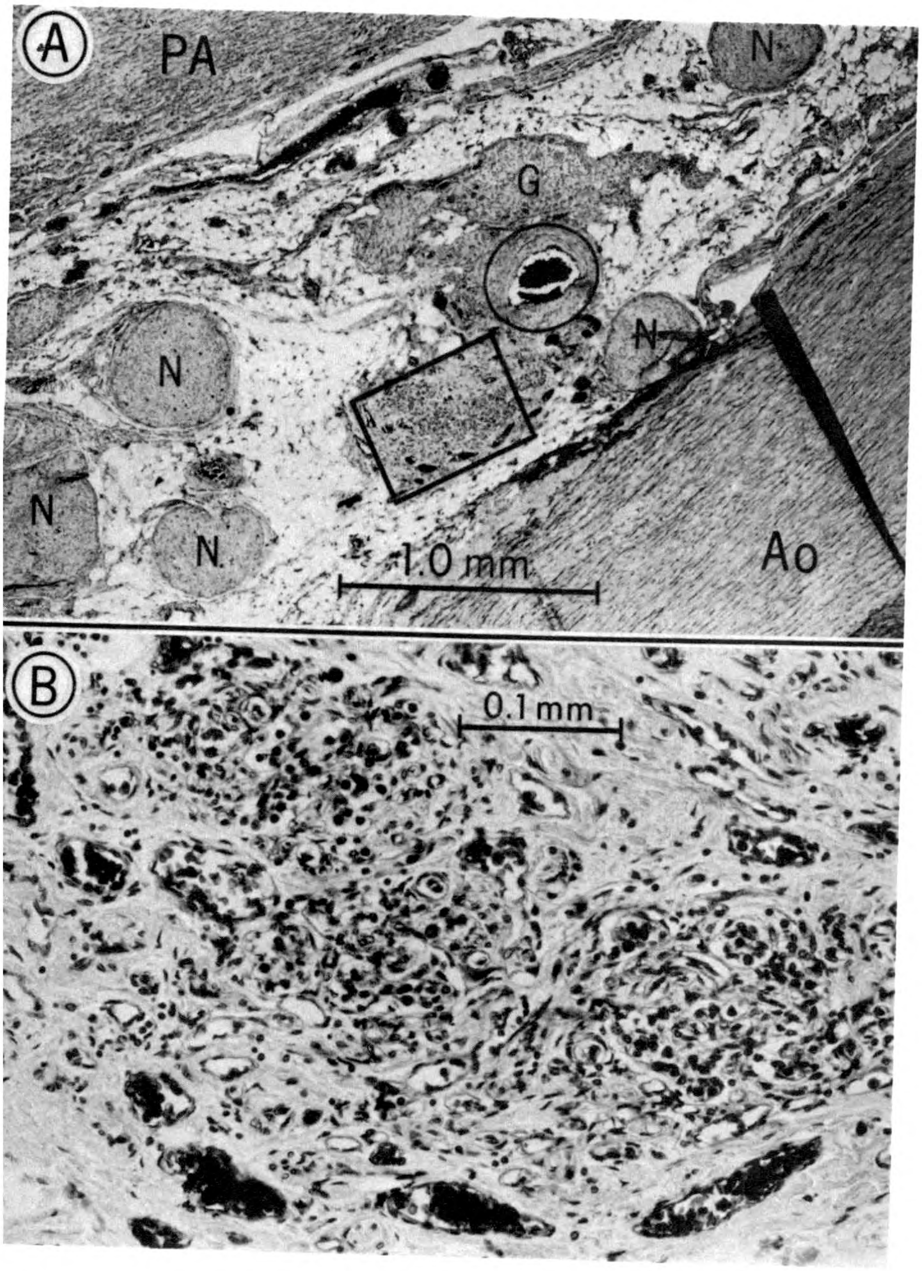

Figure 8. This photomicrograph depicts histologic appearance of a normal coronary chemoreceptor (boxed in **A** and shown at higher magnification in **B**). Chemoreceptor artery is circled in A. The abundance of neighboring nerves (N) and a ganglion (G) is apparent within the intertruncal space between aorta (Ao) and pulmonary artery (PA). Magnifications are indicated with reference bars. Specimen was from an adult man with no cardiovascular disease. (Goldner trichrome stain.)

linical Significance of the Cardiogenic ypertensive Chemoreflex

hat which drew my attention and interest to this eflex early on is the development of new hyperten- on of a severe degree among some patients with cute myocardial infarction or angina pectoris. It was ardly an original observation, since in 1931 Sir homas Lewis had reported this clinical association which he applied the colorful term of "autonomic orms" (32). A short time later Levine and Ernstene emonstrated that the hypertension preceded the nginal pain and was not caused by it (33). Later still, orwitz and Sjoerdsma documented the temporal relationships in an even more systematic fashion (4). Although the new hypertension is not always severe, levels of 240/160 mm Hg are not unusual in such cases.

Teleological reasons for the existence of a cardiogenic hypertensive chemoreflex, particularly as may be observed during the clinical course of ischemic heart disease, include the following. Virtually all the circulating serotonin is normally bound in the platelets (34). Platelet aggregation is classically associated with clinically active coronary disease, and serotonin (along with several other vasoactive substances) is released at those times. The concentration of seroto-

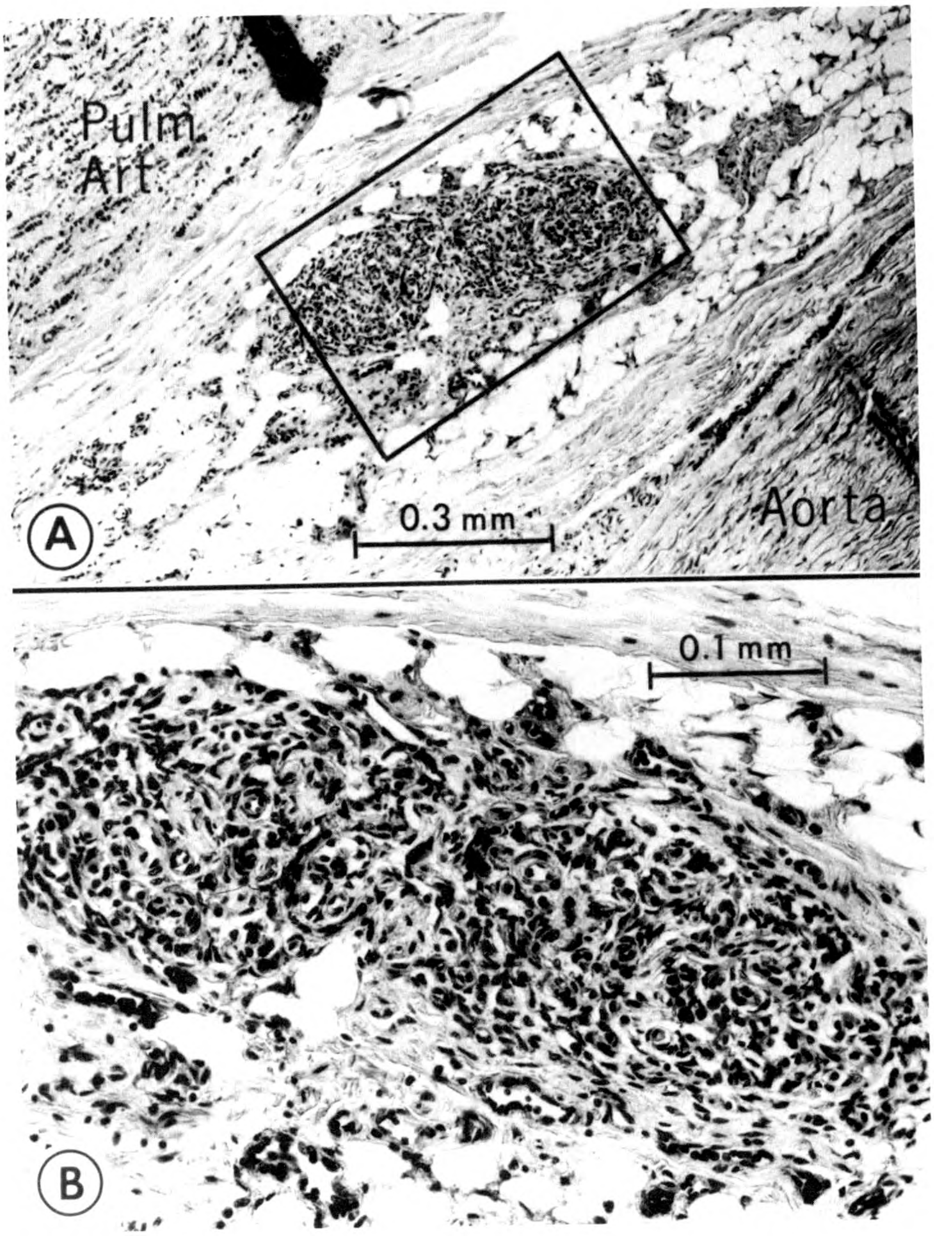

Figure 9. A second example of normal coronary chemoreceptor is illustrated here, also from the heart of a man without cardiac disease. The chemoreceptor (glomus) in **A** is boxed and shown at higher magnification in **B**. The morphology closely resembles normal carotid body. (Goldner trichrome stain.)

nin potentially released by 1 mL of aggregating platelets in humans can be reasonably estimated to be at least 2000 μg (7), whereas maximal experimental response may be elicited with about one-tenth this amount of serotonin administered to a dog. Finally, if platelets are aggregating in or near the main left coronary artery, it would be useful if they could be dislodged or disaggregated, and a sudden sharp increase in blood pressure could admirably suit this purpose.

To examine how often anterior myocardial infarction and proximal left coronary disease could be found among patients with new hypertension during acute myocardial infarction, we reviewed the coronary arteriograms of a group of such patients (13), anticipating that those with new hypertension might have predominant or exclusive proximal left coronary disease. What we found was that the location of the infarct and of coronary disease was not correlated in that fashion. However, in every patient with new hypertension during an acute myocardial infarction, there was significant proximal left coronary disease present. It was probably naive to expect the initial correlation which we anticipated, since "infarction at a distance" and other paradoxes in attempting to relate coronary lesions to location of infarction have historically been frustrating. Put another way, in patients with clinically significant coronary disease,

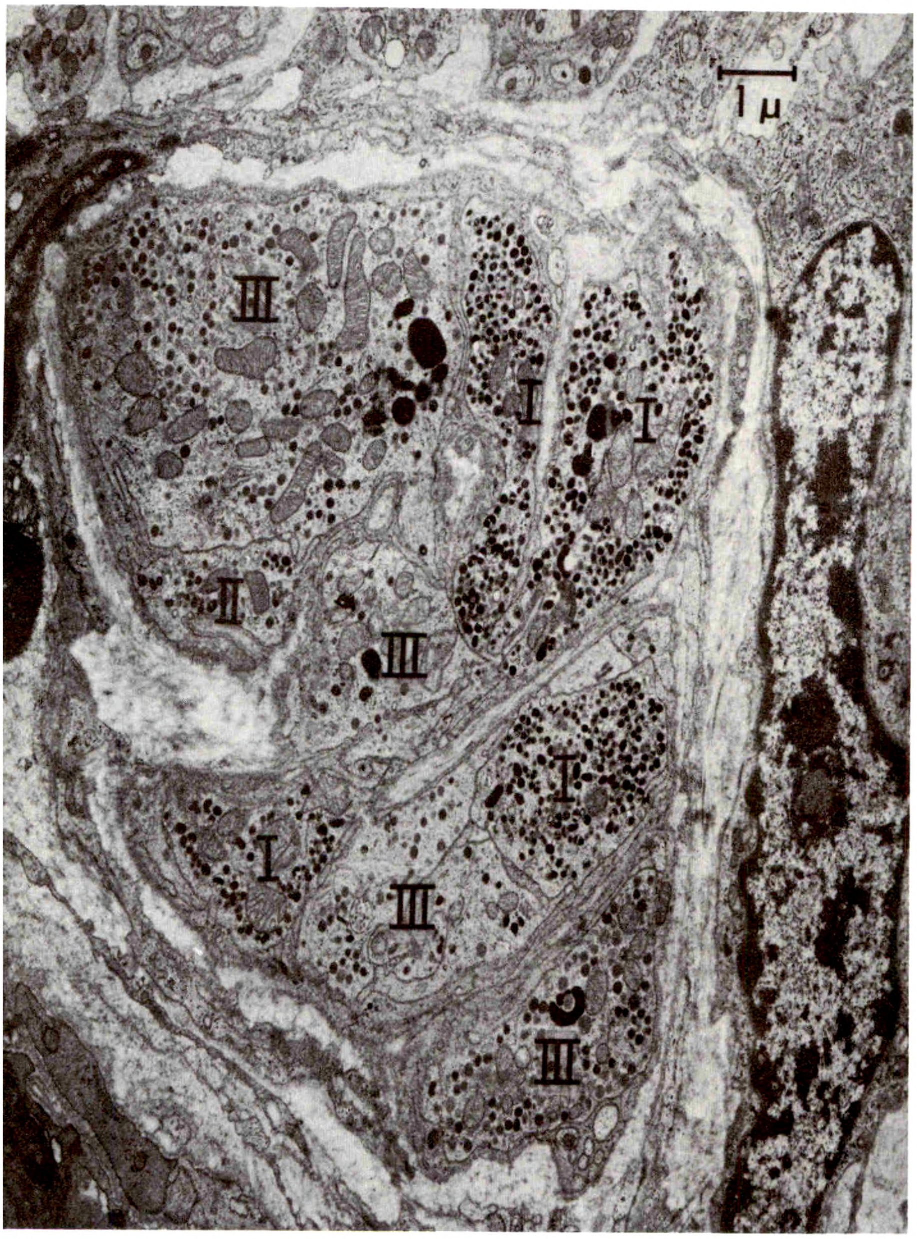

Figure 10. This electron micrograph of a feline coronary chemoreceptor depicts three types of chief cells, graded according to relative prevalence of dark and light intracellular granules. (With permission from ref. 15.)

involvement of multiple sites is the rule. Furthermore, there are probably widespread sites of platelet aggregation in patients at these times and, even teleologically, it would be helpful to dislodge aggregating platelets throughout the coronary tree, not only the left coronary. Nevertheless, some have demonstrated a relationship between anterior myocardial nfarction and new hypertension (23,35,36), as well as the more familiar relationship between the Bezold–arisch response and acute posterior infarctions.

Another possible relation of the cardiogenic hyperensive chemoreflex to coronary disease may exist in he new hypertension so often observed postoperaively and now widely investigated among patients after coronary artery bypass graft surgery, aortic valve replacement, and other procedures with cardiopulmonary bypass (15,37–61). Many of these procedures, especially coronary artery bypass grafting or aortic valve replacement, include manipulation within or near the intertruncal space. There are several possible explanations for this postoperative hypertension, each of which can be challenged as not fully satisfying. However, the strength of evidence to support a neurogenic etiology has led to efforts by some groups to treat or block the hypertension by local anesthesia of the stellate ganglion (60,61).

More direct evidence to implicate the coronary chemoreceptor in some of these problems in coronary

Figure 11. These drawings illustrate the procedure of plexectomy, in which all intertruncal neural elements are surgically removed, inevitably including the coronary chemoreceptor tissue. See text for discussion. (With permission from ref. 62.)

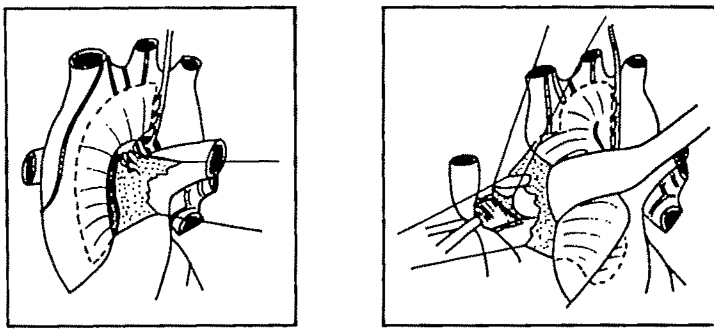

Fig. 1.—Step 1: preaortic dissection.

Fig. 3.—Step 2: retroaortic dissecti

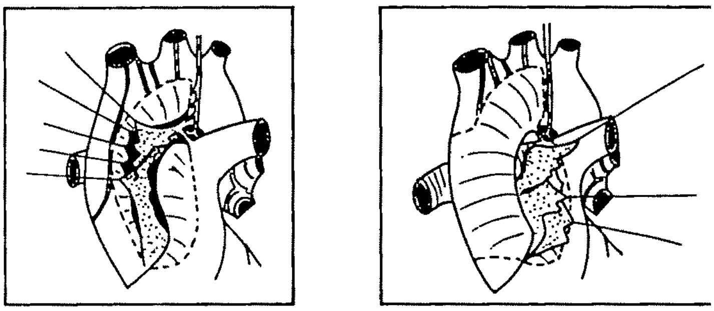

Fig. 2—Step 1: prepulmonary dissection.

Fig. 4—Step 3: subaortic dissectio

disease and in postoperative hypertension exists from the experience of Soots et al. and their plexectomy procedure (62). Originally intended as a means of treating patients with variant angina and coexisting coronary disease, they achieved a remarkable degree of success (>90%) in relieving angina by removing all the neural elements within the intertruncal space (Figure 11). Furthermore, when they encountered catastrophic occurrence of irreversible ventricular fibrillation during their initial manipulation of the intertruncal tissues in a few early cases, they decided to infiltrate the intertruncal region and produce local anesthesia, with the result that they completely eliminated this problem in subsequent cases. Although they did not report personal experience with the anatomical substrate, instead depending on previous descriptions by others, there is no question that plexectomy must include the coronary chemoreceptors, along with many other adjacent neural elements. In earlier studies my colleagues and I were able to eliminate both the Bezold–Jarisch reflex (63), as well as the cardiogenic hypertensive chemoreflex (7), by local infiltration of the intertruncal space with lidocaine (Figure 12).

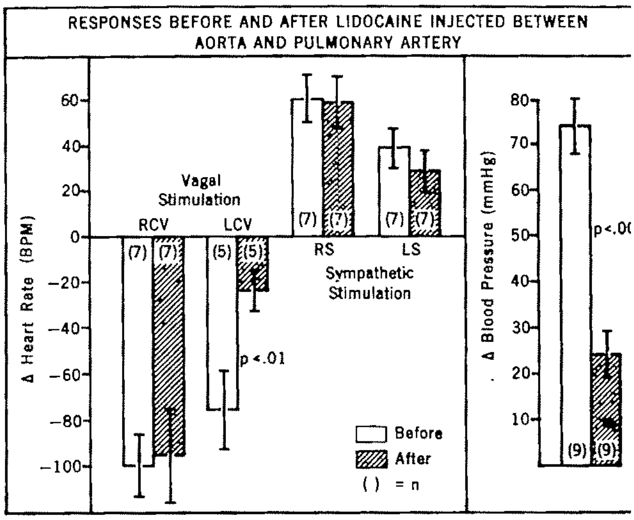

Figure 12. Local anesthesia produced by interstitial injection int the intertruncal space effectively blocks the cardiogenic hyperten sive chemoreflex. For comparison, the responses to electric stimulation of the cervical vagal trunks or stellate ganglia ar unchanged except possibly the left cervical vagus.

Others have demonstrated that plexectomy was not helpful in three patients who had variant angina but no angiographic evidence of coronary disease, and they recommended that the procedure not be done in that category of patients (64). Although the purpose of the Soots plexectomy was an expectation that coronary spasm might be prevented, it may be noted that our experimental studies in dogs demon strated no influence on the coronary circulation dur ing the cardiogenic hypertensive chemoreflex (9). O course, absence of coronary vasoconstriction in th dog may not be true in humans, particularly whe coronary disease is superimposed. But there is als the interesting possibility that angina might be re lieved (as it was in the experience of Soots et al independent of any direct effect on the coronar circulation.

With Rossi and Hageman we have examined the likelihood that anginal pain is mediated via neural elements within the intertruncal space and particularly the coronary chemoreceptor (65). Human evidence included thrombotic occlusion of the chemoreceptor artery and the presence of fibrotic destruction of the coronary chemoreceptor in two fatal cases of coronary disease in which angina had abated or was absent within weeks before death, in one patient after coronary bypass surgery. Experimentally, awake dogs respond to serotonin administration into the left atrium not only with the usual abrupt hypertension but also with a number of signs suggestive of angina (65), such as stretching of the forelegs, plus visible apprehension and anxiety, including whining and tremulousness. Because there is no way to know exactly how a dog would perceive angina and respond to it, one can only conjecture about the significance of these observations, but they are supportive of the idea. If the coronary chemoreceptor and the reflex that it produces are involved in the pathogenesis of angina pectoris, and a vagal afferent pathway is involved, as several clinical observations suggest (65), this would be very different from the prevalent or conventional belief that sympathetic afferents are responsible for angina pectoris (66–69).

Patients with Takayasu's aortitis (70,71) or with polyarteritis nodosa do not require still another explanation for their frequently observed hypertension because renal disease or other problems may be sufficient, but the possibility of involvement of the arteries in and near the coronary chemoreceptor merits additional consideration. Chemoreceptor arteritis can be especially suspected when hypertension with aortitis is paroxysmal rather than sustained (71). Amyloidosis has been documented to be severely destructive to the coronary chemoreceptor (72), from which one may suspect that the postural hypotension sometimes observed in patients with amyloidosis could be related to the chemoreceptor disease. However, the additional involvement of many different neural elements and of the vascular walls themselves by amyloid infiltration obviously contributes to the problem.

One may ask why hypertension is not seen more often among patients with carcinoid disease, a clinical condition notably associated with liberation of serotonin by the tumor. Of course, several other vasoactive substances are also released by such tumors (73,74), and any of these may directly or indirectly affect blood pressure to raise or lower it. Furthermore, most of these patients at the time of diagnosis typically have moderate or severe diarrhea and other physiological problems that may alter blood volume or pressure or both. Tumors with prominent influence upon blood pressure do not typically release their vasoactive material steadily but rather almost always do so episodically; pheochromocytoma is a classic example of this. When serotonin levels have been measured in the blood of patients with carcinoid disease, they may be as much as ten times the normal level (75), but even those levels are only about one-hundredth the concentration of serotonin used experimentally in the dog to elicit the hypertensive response (7). However, the measurements done in carcinoid patients without hypertension at the time may not be representative of serotonin blood levels in patients with hypertension, of whom a large number of examples have now been reported (76). Among these have been carcinoid patients who had blood pressures fluctuating between 200/102 and 224/118 mm Hg (77), between 130/70 and 188/106 (78), and between 110/80 and 292/156 (75). Additionally, in studies of the basis for the typical cutaneous flush observed in patients with carcinoid disease, Robertson et al. (79) administered serotonin intravenously to 11 subjects and had to discontinue the study in 3 individuals because the intravenous serotonin produced a "pressor response." It has already been suggested by some (76,80) that hypertension may be as frequent as hypotension in association with carcinoid disease, and careful future studies may demonstrate that hypertension is not so much rare as unrecognized. If that proves to be true, one could interpret it as an experiment of nature producing the cardiogenic hypertensive chemoreflex in human beings.

There are tumors that involve the intertruncal space and produce hypertension of a marked degree, which is easily understood when some of them have been found to be pheochromocytoma (81–88). In fact, there is a surprising number of surgical reports precisely describing tumors in or near the interatrial septum, the main left coronary artery, or the intertruncal space (86–88). Future investigation of such cases should include consideration of involvement of the coronary chemoreceptor as well as other neural elements in the region. Additionally, there is the infrequent but puzzling occurrence of small masses of thyroid tissue in the intertruncal space (89–92), but whether this relates to normal or abnormal function of the coronary chemoreceptor in any way is unknown.

As is evident from experimental observations (7) and clinical evidence during surgery for plexectomy (62), activation or surgical manipulation of the coronary chemoreceptor and nearby neural elements can be associated with a wide variety of electrical disturbances of the heart (Figure 4). Because terminal electrical instability of the heart is the probable cause of many and possibly most cases of sudden unexpected death, it is hardly surprising that pathological changes in the coronary chemoreceptor and nearby neural elements are a frequent finding in cases of otherwise unexplained sudden death (16). The variety of histopathology in such cases includes foci of inflammation or degeneration as well as older fibrotic destruction; local narrowing of nutrient arteries accompanies those changes in some cases.

Future Questions and Studies

Local anesthesia of the intertruncal space will block both the Bezold–Jarisch reflex (63) as well as the cardiogenic hypertensive chemoreflex (7), two responses that are almost mirror images of each other. The former causes bradycardia, heart block, and hypotension, whereas the latter causes marked hypertension and mixed vagal and sympathetic influence on the electrical and mechanical activity of the heart. One may question whether the same response to local anesthesia explains the effective blockade of two such different reflexes, although it may be noted that both reflexes are mediated by an afferent vagal pathway. At present the more plausible explanation is that sensory receptors throughout the ventricular myocardium are activated in the Bezold–Jarisch reflex (93–94), and their final common pathway out of the heart is via the intertruncal space (63), so that the afferent neural pathway is anesthetized. For the cardiogenic hypertensive chemoreflex it seems likely that either the local anesthesia renders the coronary chemoreceptor unresponsive, or its afferent nerves are blocked, or both.

At an even more fundamental level one can ask how the cardiogenic hypertensive chemoreflex is actually mediated within or near the coronary chemoreceptor. Is the administered serotonin directly responsible, or does it release a local mediator within the glomoid tissue, perhaps from granules within the chief cells? And whatever the chemical mediator may be, does it act on nearby neural endings within the coronary chemoreceptor, or directly on the chief cells themselves as the ultrastructural appearance of synapses suggests (15)? Of the many nerves and ganglia within the intertruncal space, which ones serve the coronary chemoreceptor, and do they intercommunicate with other nerves and ganglia or with nearby baroreceptors? There are neuroreceptors in the heart that function through an afferent pathway by way of sympathetic nerves and the spinal cord (95,96). How do these different reflexes integrate with the events of the cardiogenic hypertensive chemoreflex, either within or near the heart, or after the afferent signals of either have reached central sites within the brain?

This raises an analogous question about possible tonic activity of the coronary chemoreceptor. Is a lesser level of the cardiogenic hypertensive chemoreflex, which is constantly present, perhaps of importance to the maintenance of normal blood pressure? Does the coronary chemoreceptor and its putative tonic activity participate in the pathogenesis of left ventricular hypertrophy, including that of idiopathic cardiomyopathy? My prior discussion has emphasized the possible role, during acute myocardial infarction, of the cardiogenic hypertensive chemoreflex in new hypertension; does loss of the coronary chemoreceptor, as might occur with certain types of coronary occlusion, have as one consequence the development of cardiogenic shock? Certainly the proximal location of blood supply to the coronary chemoreceptor would suggest that it might be included in the massive ischemic insult following main left coronary occlusion.

Whether ischemia of the coronary chemoreceptor would activate the cardiogenic hypertensive chemoreflex is uncertain because of the difficulty in separating the effect of ischemia from the effect of serotonin liberated from platelets included in clot formation, which in turn is the usual cause of cardiac ischemia. In their classic study, Eckstein and his colleagues (6) performed temporary occlusion of the small coronary branch supplying the chemoreceptor and observed a pressor response, but whether that was caused by serotonin released from platelets aggregating just beyond the ligature or by the ischemia is unclear, and the two possible causes would be difficult to separate. Knowing that serotonin is itself so powerful in eliciting the cardiogenic hypertensive chemoreflex *without* any accompanying ischemia, it seems more reasonable for the present to attribute any possible clinical counterpart, such as might occur in patients with known ischemic heart disease, to the effect of serotonin either alone or possibly in conjunction with glomoid ischemia.

During surgery and in the postoperative period of certain cases, should cyproheptadine be administered to prevent or reverse new hypertension? In that context it should be noted that methysergide is ineffective in blocking the cardiogenic hypertensive chemoreflex in the dog, and we have not found ketanserin to be effective in preliminary studies, but for both these agents it is well to keep in mind potential species differences for responses in humans. Soots and his colleagues in France no longer perform plexectomy for treating variant angina, since newer pharmacological approaches are quite satisfactory (personal communication). However, the possible protective effects of local intertruncal anesthesia before or during certain cardiac operations may merit investigation. If the role of the cardiogenic hypertensive chemoreflex proves in future studies to be important in essential hypertension, in malignant hypertensive crises, or in idiopathic cardiac hypertrophy, one may speculate that plexectomy could be reconsidered for a different useful purpose than was originally intended.

Nonspecific activation of the cardiogenic hypertensive chemoreflex with nicotine or similar nonphysiological alkaloids may represent susceptibility of the chemoreceptor to agents other than serotonin, and some have been suggested by others (97). In our original studies we examined several other neurotransmitters and vasoactive agents as possible candidate agonists and found them to be ineffective (7); however, there may well be other normally occurring substances effective as agonists or antagonists, and this merits further study.

Idiopathic orthostatic hypotension, or the hypotension associated with amyloidosis or with diabetic autonomic neuropathy, may involve a number of the intertruncal neural elements, including the coronary chemoreceptor. In fact, the exact identification of specific function by these abundant and varied neural structures present within the intertruncal space may be one of the most intriguing subjects for future neurophysiological research, and the prospect of direct clinical usefulness of the findings is most attractive.

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References

1. Katholi RE, Oparil S, Urthaler F, James TN. The mechanism of postarrhythmic renal vasoconstriction in the anesthetized dog. J Clin Invest 1979;64:17–31.
2. Katholi RE, Bishop SP, Oparil S, James TN. Renal function during reflexly activated catecholamine flow through an adrenorenal rete. Am J Physiol 1981;240:F30–7.
3. Comroe JH Jr. The location and function of the chemoreceptors of the aorta. Am J Physiol 1939;127:176–91.
4. Horwitz D, Sjoerdsma A. Some interrelationships between elevation of blood pressure and angina pectoris. Hypertension XIII. Proceedings of the Council for High Blood Pressure Research. New York: American Heart Association, Inc., 1965: 39–48.
5. Becker AE. The glomera in the region of the heart and great vessels. Pathol Eur 1966;1:410–24.
6. Eckstein RW, Shintani F, Rowen HE Jr, et al. Identification of left coronary blood supply of aortic bodies in anesthetized dogs. J Appl Physiol 1971;30:488–92
7. James TN, Isobe JH, Urthaler F. Analysis of components in a cardiogenic hypertensive chemoreflex. Circulation 1975;52: 179–92.
8. Hageman GR, Urthaler F, James TN. Neural pathways of a cardiogenic hypertensive chemoreflex. Am J Physiol 1978; 235:H345–9.
9. Urthaler F, James TN, Hageman GR. Regional flow patterns during the serotonin-induced cardiogenic hypertensive chemoreflex. Cardiovasc Res 1980;14:169–76.
10. Urthaler F, Hageman GR, James TN. Hemodynamic components of a cardiogenic hypertensive chemoreflex in dogs. Circ Res 1978;42:135–42.
11. Hageman GR, James TN, Urthaler F. Studies of changes in breathing and blood pressure accompanying a cardiogenic hypertensive chemoreflex compared in conscious and anesthetized dogs. Am Heart J 1983;106:547–53.
12. Hageman GR, Coghlan HC, James TN, Neely BH. Influence of atrial mechanoreceptors upon the sympathetic efferent activity elicited during a cardiogenic chemoreflex in the dog. J Auton Nerv Syst 1983;9:637–44.
13. Dye LE, Urthaler F, MacLean WAH, Russell RO, Rackley CE, James TN. New arterial hypertension during myocardial infarction. South Med J 1978;71:289–92.
14. Wallach R, Karp RB, Reves JG, Oparil S, Smith LR, James TN. Pathogenesis of paroxysmal hypertension developing during and after coronary bypass surgery: a study of hemodynamic and humoral factors. Am J Cardiol 1980;46:559–65.
15. Imamura K, James TN, Scully KT, Hageman GR, Urthaler F. Ultrastructure of a coronary chemoreceptor of dogs and cats. J Mol Cell Cardiol 1982;14:711–24.
16. James TN. Degenerative lesions of a coronary chemoreceptor and nearby neural elements in the hearts of victims of sudden death. Trans Am Clin Climatol Assoc 1985;97:158–74.
17. Von Bezold A, Hirt L. Von der Wirkung des Veratrins auf den Kreislauf. Untersuch Physiol Lab Würzburg 1867;1:95–115.
18. Zucker IH, Cornish KG. The Bezold–Jarisch reflex in the conscious dog. Circ Res 1981;49:940–8.
19. Mark AL. The Bezold–Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. J Am Coll Cardiol 1983;1:90–102.
20. Juhasz-Nagy A, Szentivanyi M. Localization of the receptors of the coronary chemoreflex in the dog. Arch Int Pharmacodyn Ther 1961;131:39–55.
21. Robertson D, Hollister AS, Forman ME, Robertson RM. Reflexes unique to myocardial ischemia and infarction. J Am Coll Cardiol 1985;5:99B–104B.
22. Schröder P, Wagner K. Zur Hypertonie bei frischem Myokardinfarkt. Med Welt 1975;26:583–7.
23. Cosin J, Gimeno V, Alegre S, Breto M, Perez-Gomez F. Reflex cardiovascular response to acute myocardial ischaemia. Cardiovasc Res 1984;18:555–60.
24. James TN, Nadeau RA. Direct perfusion of the sinus node: an experimental model for pharmacologic and electrophysiologic studies of the heart. Henry Ford Hosp Med Bull 1962;10:21–5.
25. James TN, Bear ES, Frink RJ, Lang KF, Tomlinson JC. Selective stimulation, suppression, or blockade of the atrioventricular node and His bundle. J Lab Clin Med 1970;76:240–56.

26. Urthaler F, James TN. Cholinergic and adrenergic control of the sinus node and AV junction. In: Randall WC, ed. Neural regulation of the heart. New York: Oxford University Press, 1977:247–88.

27. Hageman GR, Urthaler F, James TN. Parasympathetic and sympathetic efferent traffic during a cardiogenic hypertensive chemoreflex. Cardiovasc Res 1984;18:583–90.

28. Kilbourne EM, Hageman GR, James TN, Urthaler F. Postexcitatory depression in thoracic sympathetic efferent neural traffic during a cardiogenic hypertensive chemoreflex. Basic Res Cardiol 1982;77:423–30.

29. Boyd JD. The inferior aortico-pulmonary glomus. Br Med Bull 1961;17:127–31.

30. Edwards C, Heath D. Site and blood supply of the intertruncal glomera. Cardiovasc Res 1970;4:502–8.

31. Coleridge HM, Coleridge JCG, Howe A. Thoracic chemoreceptors in the dog. A histological and electrophysiological study of the location, innervation and blood supply of the aortic bodies. Circ Res 1970;26:235–47.

32. Lewis T. Angina pectoris associated with high blood pressure and its relief by amyl nitrate; with a note on Nothnagel's syndrome. Heart 1931;15:305–27.

33. Levine SA, Ernstene AC. Observations on arterial blood pressure during attacks of angina pectoris. Am Heart J 1933; 8:323–6.

34. Costa JL, Reese TS, Murphy DL. Serotonin storage in platelets: estimation of storage-packet size. Science 1974;183:537–8.

35. Perez-Gomez F, Martin De Dios R, Rey J, Garcia-Aguado A. Prinzmetal's angina: reflex cardiovascular response during episode of pain. Br Heart J 1979;42:81–7.

36. Perez-Gomez F. Clinical cardiovascular response to ventricular reflexes with special reference to myocardial ischemia. Clin Cardiol 1978;1:125–9.

37. Estafanous FG, Tarazi RC, Viljoen JF, El Tawil MY. Systemic hypertension following myocardial revascularization. Am Heart J 1973;85:732–8.

38. Fouad FM, Estafanous FG, Tarazi RC. Hemodynamics of postmyocardial revascularization hypertension. Am J Cardiol 1978;41:564–9.

39. Fouad FM, Estafanous FG, Bravo EL, Iyer KA, Maydak JH, Tarazi RC. Possible role of cardioaortic reflexes in postcoronary bypass hypertension. Am J Cardiol 1979;44:866–72.

40. Flaherty JT, Magee PA, Gardner TL, Potter A, MacAllister NP. Comparison of intravenous nitroglycerin and sodium nitroprusside for treatment of acute hypertension developing after coronary artery bypass surgery. Circulation 1982;65:1072–7.

41. Gray RJ, Bateman TM, Czer LSC, Conklin C, Matloff JM. Comparison of esmolol and nitroprusside for acute post-cardiac surgical hypertension. Am J Cardiol 1987;59:887–91.

42. Reves JG, Karp RB, Buttner EE, et al. Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. Circulation 1982;66:49–55.

43. Patel CB, Laboy V, Venus B, Mathru M, Wier D. Use of sodium nitroprusside in post-coronary bypass surgery. A plea for conservatism. Chest 1986;89:663–7.

44. Niarchos AP, Roberts AJ, Case DB, Gay WA Jr, Laragh JH. Hemodynamic characteristics of hypertension after coronary bypass surgery and effects of the converting enzyme inhibitor. Am J Cardiol 1979;43:586–93.

45. McQueen MJ, Watson ME, Bain WH. Transient systolic hypertension after aortic valve replacement. Br Heart J 1972;34: 227–31.

46. Layton C, Monro J, Brigden W, McDonald A, McDonald L, Weaver J. Systemic hypertension after homograft aortic valvar replacement. A cause of late homograft failure. Lancet 1973; 2:1343–7.

47. Whelton PK, Flaherty JT, MacAllister NP, et al. Hypertension following coronary artery bypass surgery. Role of preoperative propranolol therapy. Hypertension 1980;2:291–8.

48. Weinstein GS, Zabetakis PM, Clavel A, et al. The renin-angiotensin system is not responsible for hypertension following coronary artery bypass grafting. Ann Thorac Surg 1987; 43:74–7.

49. Viljoen JF, Estafanous FG, Tarazi RC. Acute hypertension immediately after coronary artery surgery. J Thorac Cardiovasc Surg 1976;71:548–50.

50. Roberts AJ, Niarchos AP, Subramanian VA, et al. Systemic hypertension associated with coronary artery bypass surgery. J Thorac Cardiovasc Surg 1977;74:846–59.

51. Roberts AJ, Niarchos AP, Subramanian VA, et al. Hypertension following coronary artery bypass graft surgery. Circulation 1978;58:I43–9.

52. Chaptal PA, Grolleau-Raoux D, Millet F, Grolleau-Raoux R. Les crises hypertensives dans la chirurgie de l'insuffisance coronarienne. Ann Chir Thorac Cardiovasc 1975;14:255–61.

53. Cooper TJ, Clutton-Brock TH, Jones SN, Tinker J, Treasure T. Factors relating to the development of hypertension after cardiopulmonary bypass. Br Heart J 1985;54:91–5.

54. Sarvotham SS. Nitroprusside therapy in post-open heart hypertensives: a ritual tryst with cyanide death? Chest 1987; 91:796.

55. Estafanous FG, Tarazi RC, Buckley S, Taylor PC. Arterial hypertension in immediate postoperative period after valve replacement. Br Heart J 1978;40:718–24.

56. van der Starre PJA, Scheijgrond HW, Reneman RS, Killing JB. The use of ketanserin, a 5-hydroxytryptamine receptor antagonist, for treatment of postoperative hypertension following coronary artery bypass surgery. Anesth Analg 1983;62:63–9.

57. Koppes GM, Jones FG. Systolic hypertension after aortic valve replacement. Cardiovasc Med 1978;3:567–9.

58. Estafanous FG, Tarazi RC, Buckley S, Taylor PC. Arterial hypertension in immediate postoperative period after valve replacement. Br Heart J 1978;40:718–24.

59. Engelman RM, Haag B, Lemeshow S, Angelo A, Rousou JH. Mechanism of plasma catecholamine increases during coronary artery bypass and valve procedures. J Thorac Cardiovasc Surg 1983;86:608–15.

60. Fee HJ, Viljoen JF, Cukingnan RA, Canas MS. Right stellate ganglion block for treatment of hypertension after cardiopulmonary bypass. Ann Thorac Surg 1979;27:519–22.

61. Tarazi RC, Estafanous FG, Fouad FM. Unilateral stellate block in the treatment of hypertension after coronary bypass surgery. Implications of a new therapeutic approach. Am J Cardiol 1978;42:1013–8.

62. Soots G, Warembourg H Jr, Stankowiak C, Watel A, Bertrand M. The place of cardiac denervation in the surgical treatment of Prinzmetal variant angina. J Cardiovasc Surg 1983;24:150–5.

63. Frink RJ, James TN. Intracardiac route of the Bezold–Jarisch reflex. Am J Physiol 1971;221:1464–9.

64. Weber S, Donzeau-Gouge G-P, Chauvaud S, et al. Assessment of plexectomy in the treatment of severe coronary spasm in patients with normal coronary arteries. Am J Cardiol 1983; 51:1072–5.

65. James TN, Rossi L, Hageman GR. On the pathogenesis of angina pectoris and its silence. Trans Am Clin Climatol Assoc 1988 (in press).

66. Cutler EC. Summary of experiences up-to-date in the surgical treatment of angina pectoris. Am J Med Sci 1927;173:613–24.

67. Malliani A, Schwartz PJ, Zanchetti A. Sympathetic reflex elicited by experimental coronary occlusion. Am J Physiol 1969;217:703–9.

68. Malliani A, Lombardi F. Consideration of the fundamental mechanisms eliciting cardiac pain. Am Heart J 1982;103:575–8.

69. Malliani A. The elusive link between transient myocardial ischemia and pain. Circulation 1986;73:201–4.
70. Teoh PC, Tan LKA, Chia BL, Chao TC, Tambyah JA, Feng PH. Non-specific aorto-arteritis in Singapore with special reference to hypertension. Am Heart J 1978;95:683–90.
71. Tanaka N, Tanaka H, Toyama Y, Kashima T, Niimura T, Kanehisa T. Paroxysmal hypertension in aortitis syndrome. Am Heart J 1975;90:369–75.
72. Volpi A, Cavalli A, Maggioni AP, Matturri L, Rossi L. Cardiac amyloidosis involving the conduction system and the aorto-coronary neuroreceptors. Chest 1986;90:619–21.
73. Plank J, Feldman JM. Adrenal function in the carcinoid syndrome: effects of the serotonin anatagonist cyproheptadine. Metabolism 1975;24:1035–46.
74. Casthely PA, Jablons M, Griepp RB, Ergin MA, Goodman K. Ketanserin in the preoperative and intraoperative management of a patient with carcinoid tumor undergoing tricuspid valve replacement. Anesth Analg 1986;65:809–11.
75. Adicoff A, Alexander CS, Davis RB. Malignant carcinoid syndrome. Serotonin concentrations and hemodynamic studies. Arch Intern Med 1966;117:250–5.
76. Manger WM, Gifford RW Jr. Carcinoid tumors. In: Manger WM, Gifford RW Jr, eds. Pheochromocytoma. New York, Heidelberg, Berlin: Springer-Verlag, 1977:154–5.
77. Steele CW. Malignant carcinoid. Metastasis to skin and production of carcinoid syndrome, hypertension, diarrhea, dementia, and hypopotassemia: a case report. Arch Intern Med 1962;110:763–8.
78. Bean WB, Funk D. The vasculocardiac syndrome of metastatic carcinoid. Arch Intern Med 1959;103:189–99.
79. Robertson JIS, Peart WS, Andrews TM. The mechanism of facial flushes in the carcinoid syndrome. Q J Med 1962;31:103–23.
80. Rosenberg EB. The carcinoid syndrome and hypertension. Arch Intern Med 1968;121:95–6.
81. Karasov RS, Sheps SG, Carney JA, van Heerden AJ, DeQuattro V. Paragangliomatosis with numerous catecholamine-producing tumors. Mayo Clin Proc 1982;57:590–5.
82. Gross JL, Azevedo MJ, Ludwig EB, de los Santos A, Pinto JF. Cardiac pheochromocytoma. Am J Med 1987;83:1013.
83. Besterman E, Bromley LL, Peart WS. An intrapericardial phaeochromocytoma. Br Heart J 1974;36:318–20.
84. Awoke S, Perlstein RS. Dopamine- and norepinephrine-secreting intrapericardial pheochromocytoma in a normotensive patient. South Med J 1985;78:994–8.
85. Shimoyama Y, Kawada K, Imamura H. A functioning intrapericardial paraganglioma (pheochromocytoma). Br Heart J 1987;57:380–3.
86. Orringer MB, Sisson JC, Glazer G, et al. Surgical treatment of cardiac pheochromocytomas. J Thorac Cardiovasc Surg 1985;89:753–7.
87. Orenstein HH, Green GE, Kancherla PL. Aortocoronary paraganglioma. Anatomic relationship of left coronary artery to paraganglia of aorta. NY State J Med 1984;84:33–6.
88. Stowers SA, Gilmore P, Stirling M, et al. Cardiac pheochromocytoma involving the left main coronary artery presenting with exertional angina. Am Heart J 1987:114:423–7.
89. Taylor MA, Bray M, Roberts WC. Aberrant thyroid gland attached to ascending aorta. Am J Cardiol 1986;57:708.
90. Shemin RJ, Marsh JD, Schoen FJ. Benign intracardiac thyroid mass causing right ventricular outflow tract obstruction. Am J Cardiol 1985;56:828–9.
91. Lo H-M, Tseng Y-Z, Tseng C-D, Chu S-H, Chuang S-M, Wu T-L. Intracardiac goiter: a cause of right ventricular outflow obstruction and successful operative therapy. Am J Cardiol 1984;53:976–8.
92. Greco-Lucchina P, Ottino GM, Avonto L, Carini G, Pozzi R, Emanuelli G. Ectopic thyroid remnants within the myocardium: an unusual case of right ventricular mass. Am Heart J 1988;115:195–8.
93. Shepherd JT. The heart as a sensory organ. J Am Coll Cardiol 1985;6:83B–7B.
94. Dawes GS. Studies on veratrum alkaloids. VII. Receptor areas in the coronary arteries and elsewhere as revealed by the use of veratridine. J Pharmacol Exp Ther 1947;89:325–42.
95. Pagani M, Pizzinelli P, Furlan R, et al. Analysis of the pressor sympathetic reflex produced by intracoronary injections of bradykinin in conscious dogs. Circ Res 1985;56:175–83.
96. Brown AM, Malliani A. Spinal sympathetic reflexes initiated by coronary receptors. J Physiol 1971;212:685–705.
97. Parker RE, Strandhoy JW. A vasoconstrictor cardiogenic chemoreflex induced by prostaglandin $F_{2\alpha}$. Am J Physiol 1981;9:H528–32.
98. James TN, Urthaler F, Hageman GR. Reflex heart block. Baroreflex, chemoreflex and bronchopulmonary reflex causes. Am J Cardiol 1980;45:1182–8.

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Review Article

The Jehovah's Witness Patient: Considerations for the Anesthesiologist

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Key Words: MEDICOLEGAL, JEHOVAH'S WITNESSES—transfusion. ORGANIZATIONS, JEHOVAH'S WITNESSES.

Physicians are frequently faced with ethical decisions in the delivery of health care to patients. With regard to certain ethical issues, it is at times difficult to make appropriate decisions because of the absence of any formal education on the subject and a lack of moral and medical consensus. One such issue is the question of blood transfusion and the Jehovah's Witness patient (1,2). Jehovah's Witnesses refuse blood or blood products because of religious beliefs. This refusal creates an ethical conflict for the physician wherein a possible lifesaving, medical course of action is unacceptable to the patient. The issue is further compounded by the lack of consistent legal norms and the changing expectations within the physician–patient relationship.

Anesthesiologists are in a particularly difficult position because they are responsible for the administration of blood and blood products perioperatively. Their position may be complicated by an agreement between the surgeon and patient that is morally and medically unacceptable to them. It is the purpose of this article to discuss the religious background of the Jehovah's Witnesses, to consider the ethical conflicts in caring for these patients, to survey the significant past legal decisions rendered concerning medical management of Jehovah's Witnesses, and to describe options on how to proceed with anesthesia care.

Religious Background

Jehovah's Witnesses as a religious sect was begun in the late 1870s by Charles Russel in Pennsylvania (3,4). Mr. Russel was able to spread his message through a journal, *Zion's Watch Tower and Herald of Christ's Presence*, the forerunner of the present-day *Watch Tower*. In 1931, the group began calling themselves Jehovah's Witnesses on the basis of the 43rd chapter of Isaiah in the Bible in which Jehovah declares to his people, "Ye are my witnesses." The sect developed as a fundamentalist group that believed in spreading its word with street corner speeches and house-to-house visits. These public displays led to hardship and oppression during the Depression and World War II because their beliefs were in opposition to acceptable social mores at that time. They refused to recognize any earthly authority, offered allegiance to God only, were conscientious objectors, and attacked the clergy of other religious denominations as being representatives of Satan.

The group has always based its beliefs on a literal reading of the Bible. They have predicted an imminent end of this world and the resurrection by God of the faithful witnesses to live a life without end on a renewed earth. This salvation is to be provided only to those who follow the strict tenets of their faith.

Not until July 1945, after a discussion in the *Watch Tower*, was it determined that blood transfusion should be forbidden as it violated God's law. This conclusion was based on the following three biblical passages:

From Genesis 9:3,4: "every moving thing that liveth shall be meat for you; even as the green herb have I given you all things. But the flesh with the life thereof, which is the blood thereof, ye shall not eat."

In Leviticus, 17:10–16: "therefore I say unto the

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children of Israel, ye shall eat the blood of no manner of flesh: for the life of all flesh is the blood thereof: whoever eateth it shall be cut off."

And, finally, Acts 15:19–21: "for it seemed to the Holy Ghost, and to us, to lay upon you no greater burden than these necessary things; that ye abstain from meats offered to idols, and from blood, and from things strangled, and from fornication: from which if ye keep yourselves ye shall do well."

The religious sect now numbers over 2 million members worldwide and the *Watch Tower* appears in 82 languages. Their religious reasons for not accepting blood are described in the manual "Jehovah's Witnesses and the Question of Blood," published by the Watchtower Bible and Tract Society (available on request at 25 Columbia Heights, Desk C, Brooklyn, New York 11201) (5). It is unclear why blood was declared forbidden in July 1945 or who came to this conclusion. Nonetheless, it is this decision that has created questions and conflicts from an ethical as well as medical-legal standpoint.

Ethical Aspects

Physicians experience a conflict of conscience when they are asked to stand by and allow a patient to die for want of a life sustaining blood transfusion. They are taught to preserve life. From the oath of Hippocrates, "The regimen I adopt shall be for the benefit of my patients according to my ability and judgement, and not for their hurt or for any wrong. . . . Whatsoever house I enter there will I go for the benefit of the sick. . . ." As stated by one author, "They (physicians) feel strongly that they cannot in conscience proceed with any form of care that is, in their judgement, substandard" (6). On the other hand, physicians wish to respect the desires of their patients. This is especially so because "who would benefit if the patient's corporal malady is cured but the spiritual life with God, as he sees it, is compromised, which leads to a life that is meaningless and perhaps worse than death itself" (7)? Is this desire to respect personal freedom, however morally justified, acceptable in an individual who is responsible for a child? Even more compelling, what is our moral duty to a child who has yet to define its own religious beliefs, but whose parents have insisted on a course that might result in the death of the child?

The refusal to have a blood transfusion by Jehovah's Witnesses cannot, as some have suggested, be considered an act of suicide (8). Witnesses want to live and they seek medical treatment voluntarily (9). They do not wish to be considered a problem, but ask to be considered a medical challenge (10). The challenge, however, may be a dilemma for the physician who is asked to treat but is not allowed to use the one effective treatment that may be necessary to save a life.

The situation appears clouded at times by a certain amount of ambiguity in their belief. A physician, who is a Jehovah's Witness, wrote in an article, "Witnesses' religious understanding does not absolutely prohibit the use of components such as albumin, immune globulins, and hemophiliac preparations; each Witness must decide individually if he can accept these" (10).

Other issues remain unclear. As observed by one author, "while the tenet is definite, absolute . . . it is difficult to learn from them what the consequences of its violation are; certainly, violation is a sin, but can that sin be forgiven? Does it taint them permanently in some way? Is guilt incurred if someone receives a transfusion against his or her will while unconscious? . . . Requests to church leaders for clarification result in different answers to some or all of these questions" (6).

The moral conflict is troublesome when the ethical principles and arguments are equally compelling in favor of different, exclusive courses of action. When the physician reveres the sanctity of life, what is correct in the patient whose life hangs in the balance and, in their minds, their life after death? Ethically, the question for some may be difficult to answer.

Legal Issues

There are several potential legal consequences of either administering blood to or withholding blood from a Jehovah's Witness. Physicians have therefore looked to existing law with hopes of guidance on this issue. Unfortunately, there is a lack of statute law covering this matter. Instead, we are left to survey case law, which itself rests on moral claims and varies on a case by case basis. It also differs on a jurisdiction basis and, as society changes, so does the law. Rather than legal guidance, we are left to interpretation as the law on the matter continues to evolve.

Minor Patients

In reviewing past case law and beginning with the children of Jehovah's Witnesses, the Jehovah's Witnesses claim, "in view of the well-recognized right of parental responsibility, the moral, principled and consistent position for a doctor is to recognize the responsibility of loving, concerned parents to make decisions for their minor children" (5). The courts have rejected this claim and to date, in all past cases where a child's life is clearly in danger, they have intervened to allow blood transfusion over the religious objections of the parents. The procedure that is typically followed when presented with a minor in extremis and as reviewed previously in the literature (11), consists of an application or petition to the judge of the appropriate court for judicial declaration that the minor is a "neglected child" and for appointment of a guardian. The application is typically filed by a representative of the hospital, usually the hospital administrator, and then medical evidence is presented by the physician or physicians concerning the necessity of blood transfusion. The presentation of medical evidence may be done by the primary care physician, the anesthesiologist, or both, if required. This may be done by telephone to the judge at his or her home, if necessary. The child may then be declared neglected due to the parents not providing proper medical care and a guardian is appointed, usually the hospital administrator, who then consents to transfusion for the child. The lawyer representing the individual or hospital who made initial application then presents a formal petition to the court during its next regular sitting.

The landmark case concerning a minor child, Prince vs Massachusetts (12) heard in January 1944, did not involve a blood transfusion but concerned a child distributing Jehovah's Witness literature on the street. The judge's decision, which has been quoted in all rulings since, is that "parents may be free to become martyrs themselves. But it does not follow they are free, in identical circumstances, to make martyrs of their children before they have reached the age of full and legal discretion when they can make that choice for themselves."

Cases that have followed in which a child received a blood transfusion over the religious objection of its parents include Morrison vs State (13) and State vs Perricone (14). The "Prince" decision was quoted, as well as the State's responsibility of "parens patriae," for directing the transfusions. In a class action suit brought by the Jehovah's Witnesses in the State of Washington vs King County Hospital (15) in June 1987, the Witnesses sought to ban permanently blood transfusion in their minor children. The suit was dismissed using the "Prince" decision that stated, "the right to practice religion freely does not include liberty to expose . . . the child . . . to ill health or death."

Court rulings have not been as consistent when it has involved elective medical procedures for minor children whose parents protest. In the case Hudson vs Supreme Court of Washington (16) decided in June 1942, the court refused to direct the elective amputation of a deformed arm of a child when the child's mother objected to the procedure. The court stated, "a court does not have power to deprive a parent of custody and control of a minor child in absence of determination, after hearing, that the parent is unfit to have custody of the child." In the case of Sampson vs Taylor (17), the court directed an elective operation on a child to include blood transfusion over the mother's religious objection as a Jehovah's Witness. The court ordered the surgery because of a concern of psychological harm to the child and stated it had the authority "to direct surgery even in the absence of risk to the physical health or life of the subject." The opposite decision was rendered in the case re Green (18), in which the court refused to direct an elective spine fusion on a child with blood transfusion if necessary, when the mother objected to the procedure on religious grounds as a Jehovah's Witness. The court declared, "the State does not have an interest of sufficient magnitude outweighing a parent's religious beliefs precluding medical treatment when the child's life is not immediately imperiled by his physical condition."

Fetal vs Maternal

In the area of fetal versus maternal rights, the courts seem to favor the fetus late in gestation as proved by Roe vs Wade (19), the Supreme Court decision in 1973 that established the State's interest in protecting the life of the unborn fetus once it has reached a viable age. This reasoning was followed and cited in the case Jefferson vs Griffin Spalding County Hospital Authority (20) in February 1981. In this case, the court directed a 39-weeks-pregnant woman with a viable fetus to undergo cesarean section because of complete placenta previa and to include blood transfusion if necessary over the religious objections of the woman.

The rights of the fetus early in gestation have not been completely addressed. In the case Taft vs Taft, (21) decided in March 1983, the court refused to direct a woman to undergo a cerclage procedure for an incompetent cervix. She had refused to do so on the basis of her religious convictions as a "born again Christian." The court reported, "no case has been cited to us, nor have we found one, in which a court ordered a pregnant woman to submit to a surgical procedure in order to assist in carrying a child not then viable to term."

Adult Patients

An individual's freedom to consent or refuse treatment is based on constitutional rights. In regard to adults who refuse blood transfusions on religious grounds, the key question for the courts is to determine whether there is any compelling State interest in the case that justifies overriding this belief (22).

The landmark case concerning adults and the necessity for consent occurred in 1914 in the case Schloendorff vs Society of New York Hospital (23). In this case, an adult patient refused consent for an operative procedure but agreed to an examination under anesthesia. Under anesthesia an operative procedure was performed. In addition, postoperatively it was discovered the patient suffered a brachial plexus injury from improper positioning. She experienced intense pain and eventually required amputation of some of her fingers. The patient lost the case because the hospital was a charity institution that received immunity from any liability. The presiding judge made a statement, however, that has been cited in many subsequent cases, that being, "Every human being of adult years and sound mind has a right to determine what shall be done with his own body. . . ."

A case decided in November 1977, Superintendent of Belchertown vs Saikewicz (24) became celebrated because it surveyed past reasons for which the courts had laid claim to a State interest and which prevailed over the individual's freedom to choose. In this case an adult was allowed to refuse medical treatment on the basis of "the right of a patient to preserve his or her right to privacy against unwanted infringements of bodily integrity in appropriate circumstances." The court went on to review and define what "circumstances" the courts had laid claim to a State's interest in the past. They included 1) the preservation of life, 2) the protection of the interests of innocent third parties, 3) the prevention of suicide, and 4) maintaining the ethical integrity of the medical profession. In cases that followed, the courts usually recognized the individual's right to choose as being superior to the State's interest if preservation of life was the only interest.

Cases that permitted refusal of blood transfusion in competent adults for religious reasons as Jehovah's Witnesses include Erikson vs Dilgard (25), Aste vs Brooks (26), and In re Estate of Osborne (27). In each case, the attempt at appointment of a conservator to order blood transfusion was considered to be an infringement of their freedom of religious practice under the Constitution. The individual's right to control his life took precedence over the only State interest the courts could lay claim to, that being the preservation of life.

In a case, United States vs George (28), the court used the State interest of maintaining the ethical integrity of the medical profession to direct a blood transfusion over the patient's objection on religious grounds as a Jehovah's Witness. They stated, "the patient voluntarily submitted himself to and insisted upon medical care. Simultaneously, he sought to dictate to treating physicians a course of treatment amounting to medical malpractice. . . . The patient may knowingly decline treatment, but he may not demand mistreatment."

The opposite decision, however, was rendered in the case Commissioner of Corrections vs Myers (29). The court held, "interests in maintaining the ethical integrity of the medical profession . . . are not controlling, since a patient's right of self-determination would normally be superior to such institutional considerations." In other words, an individual's right to choose will prevail when the only State interest is maintaining the ethical integrity of the medical profession.

In the case Application of the President and Directors of Georgetown College (30), the presiding judge ordered a blood transfusion for an adult patient over the objection of the patient and family based on "The patient . . ., was the mother of a seven-month-old child. The State, . . ., will not allow a parent to abandon a child, . . . the patient had a responsibility to the community to care for her infant. Thus the people had an interest in preserving the life of this mother." Therefore, the protection of the interests of innocent third parties prevails over an individual's expression of religious freedom.

Incompetent Adult Patient: Emergency Situation

The emergency situation with regard to the unconscious adult demonstrates consistent case law. It appears that when treatment is necessary to save a patient's life, a physician has a legally recognized duty to proceed. The landmark case regarding the emergency situation was decided in July 1912. The case, Luka vs Lowrie (31), involved a patient who suffered an injured foot and lost consciousness on arrival at the hospital. The attending physician amputated the patient's foot, in his opinion, to save the patient's life. The patient sought damages against the physician for lack of consent. The court ruled in favor of the physician stating, "Physicians in the nature of things are sought for and must act in emergencies, and, if a surgeon waits too long . . . he must be held to have known the consequences of such delay, and may be held liable for the resulting damage."

This reasoning was followed in the case Collins vs Davis (32) to direct surgical operation and transfusion of blood if necessary in a comatose patient over the religious objections of the patient's spouse as a Jehovah's Witness.

A similar decision was reached in February 1971 in the case of John F. Kennedy Memorial Hospital vs Heston (33). The court directed surgical operation and transfusion of blood if necessary in a comatose patient over the objection of the patient's family based on their religious belief as Jehovah's Witnesses. The court founded their decision on "There is no constitutional right to choose to die." In addition, they determined the hospital and staff are involuntary hosts of the emergency patient. As involuntary hosts, when their interests are pitted against the belief of the patient, "the hospital and staff must be allowed to pursue their functions according to their professional standards."

Competent Adult Patient: Emergency Situation

The last case to be discussed, Holmes vs Silver Cross Hospital (34), occurred in January 1972 and involved an urgent situation with a conscious and competent patient who informed his physicians he refused blood transfusion based on his religious beliefs as a Jehovah's Witness. The physicians agreed, but when the patient became unconscious they went to the court and received direction to transfuse the patient, who was declared incompetent. The family was not notified until after the transfusion was administered. The court ruled in favor of the plaintiff stating the deceased's civil rights were violated and the manner in which the transfusion order was obtained deprived the deceased and family due process of law.

Summary

From the legal survey of case law, it is apparent the courts have consistently intervened to allow blood transfusion in life threatening situations in minors over the objections of their parents. The consistency is not present, however, in strictly elective situations involving minors. In the issue of fetal versus maternal, the courts have ruled in favor of the fetus once it reaches a viable age. In the case of emergencies involving incompetent adults, the courts have consistently directed blood transfusion. The courts have not been consistent, however, with decisions regarding emergency care of competent adults. Finally, in elective cases involving an adult, the courts typically rule that every individual of sound mind and sufficient age has the legal right of self-determination in medical matters. The only exception in recent years seems to be when there is a State's interest to protect innocent third parties, typically minor children.

Society's expectations of physicians, especially in recent years, seemingly dictates the practice of medicine. A course of action or nonaction may have legal consequences. From the survey of case law and related articles concerning Jehovah's Witnesses, words like negligence, assault, battery and abandonment have been mentioned. This would, it appears, make the legal concern a relevant issue when it involves a Jehovah's Witness patient.

Medical Considerations

The decision to care for the Jehovah's Witness patient begins first with the hospital. The hospital may make the decision not to accept these patients at all, to accept these patients and their stipulation of no blood transfusions, or to seek legal intervention to permit blood transfusions when considered necessary by the physicians involved. When legal intervention is deemed necessary, the appropriate presiding judge must be petitioned to assign guardianship, usually to the hospital administrator, for consent to transfuse blood or blood products, or both. The mechanism for contacting the appropriate court or judge should be available in the hospital emergency room and operating room. From the options available to a hospital, the decision becomes a difficult one given the ethical and possible legal ramifications as well as differing opinions of individuals required to make the decision. The work of an ethics committee in formulating a hospital policy concerning the Jehovah's Witnesses and blood transfusion is described in the literature (35).

The physicians must also make a decision after considering their own beliefs, ethical concerns, and possible legal consequences. One is left with three options: First, one may ethically and legally refuse to care for these patients when they are seeking elective medical assistance. Second, one may proceed with their care with legal assistance to allow blood transfusion in basically the emergent or minor patient. Third, one can proceed with the agreement not to transfuse blood, even if it results in the death of the patient.

Table 1. Summary of Special Techniques Used

Author	Reference	Type of procedure	No. of patients	Deliberate hypotension	Deliberate hypothermia	Hemodilution	Autotranfusion	Remarks
Ott et al.	37	Cardiovascular	542		X	X		51 deaths, 15 related to blood loss
Henderson et al.	38	Cardiovascular	31		X	X	X	7 deaths, 3 related to blood loss
Bonnett et al.	39	Total hip replacement	90	—none reported—				1 death unrelated to blood loss
Nelson et al.	40	Total hip replacement	100	X				No deaths
Bonakdar et al.	41	Gynecologic and obstetric	165	—none reported—				No deaths
Smith	42	General surgery	96	—none reported—				2 deaths unrelated to blood loss; excessive surgical complications reported
Schaller et al.	43	Major cancer surgery	25	X	X	X	X	No deaths

Previous Experiences

There are several reports in the literature describing experience in caring for Jehovah's Witness patients for a variety of surgical procedures where blood transfusion was not used. This includes a case report describing a heart transplant in a Jehovah's Witness patient (36). A summary of the reports involving larger groups of Jehovah's Witness patients and the special techniques used in the anesthetic management of these patients is presented in Table 1. The report involving the largest group of patients is a retrospective study describing cardiovascular operations on 542 Jehovah's Witness patients without blood transfusion and whose ages varied from 1 day to 89 years (37). Hemodilution and deliberate hypothermia were used in the management of patients who required cardiopulmonary bypass. In this series, there were 51 deaths, 15 of them in patients in whom blood loss likely contributed to death. Another report (38) describing cardiovascular operations in Jehovah's Witness patients reviewed 36 cases that occurred during a 15-year period. Special techniques used in the management of these patients included hemodilution, deliberate hypothermia, and autotransfusion. In this series, there were seven deaths, three of them in patients in whom blood loss was directly related to the cause of death. Two reports are available describing total hip replacements in Jehovah's Witness patients, one reporting on 90 patients (39) and one reporting on 100 patients (40). Both reports described a reduction of blood loss when compared with that of controls and attributed this to factors such as operative approach, meticulous hemostasis, and/or hypotensive anesthesia. No significant differences in morbidity were reported. Another study (41) described a retrospective report of 165 Jehovah's Witnesses and 164 control patients who underwent major obstetric and gynecologic surgery. No differences in operative morbidity or mortality were found and no special techniques were described in the management of these patients. A study that reviewed 96 Jehovah's Witness patients who had undergone general surgery during a 28-year period reported an excessive rate of surgical complications (42). This rate was compared with those of surgical complications in other past studies in the literature. No speculation on why this occurred was provided. In this series there were two deaths that were unrelated to blood loss. One report (43) describes major cancer surgery in 25 infants and children, 4 of whom were Jehovah's Witnesses. There were no deaths in this series. No anesthetic or surgical complications were described in the Jehovah's Witness patients. Special techniques used in the management of these patients included deliberate hypotension, deliberate hypothermia, hemodilution, and autotransfusion.

Preoperative Management

When one agrees to provide anesthesia care for the Jehovah's Witness patient under their terms, meaning without the option of blood transfusion, the anesthesiologist's involvement with the patient must begin early. It begins with a discussion with the patient and his or her family to explore their commitment, which does vary among these patients, and then explain options and find out what they are willing to accept (44). Once one agrees to proceed with care under the limitations imposed by the patient's desires, these limitations must be respected. To agree to proceed with the intent of administering blood when the patient is unconscious under anesthesia is ethically unacceptable and legally constitutes battery (45).

The patient must then sign a consent documenting refusal of blood and absolving the physicians, the hospital, and all its employees of any liability should an untoward event occur related to his or her refusal. The Jehovah's Witness patient oftentimes carries with him or her a consent, but if not, the hospital should have their own form or the form written by the American Medical Association may be used (46). This consent, in whatever form, must be executed. The document appears to be binding and offers protection as noted by Judge Warren Berger, former Chief Justice of the Supreme Court, who observed that a malpractice proceeding would appear unsupported in which such a waiver had been signed (47). In addition, the consent should be witnessed and signed by a relative of the patient, especially when a minor or spouse is involved. This may possibly prevent a suit instituted by the executor of the estate or the closest relative in the event of the patient's death.

In operative procedures where transfusion would generally be likely, the patient's hemoglobin level should be optimized with oral iron therapy for several weeks before surgery. The ideal preparation would be preoperative removal of blood and storage for autologous transfusion during surgery (48). Few allow this, however, because most Jehovah's Witnesses require that their blood remain in a continuous circuit with their body (49, 50). One case report in the literature describes preoperative removal of blood after agreement of the patient, but who later decided against the retransfusion after discussion with other Jehovah's Witnesses (51). This left the physicians with an already anemic patient just before surgery. For this reason the explanation should be clear and detailed.

Intraoperative Management

When significant intraoperative blood loss is expected, e.g., 20% or more of total blood volume, special techniques may be employed. These include deliberate hypotension, deliberate hypothermia, hemodilution, and autotransfusion.

Deliberate hypotension is a valuable technique to employ intraoperatively for the Jehovah's Witness patient because, foremost, it reduces surgical blood loss (52,53). Its use in the Jehovah's Witness patient has been described previously (40,43). The considered safe induced lower limit of mean arterial blood pressure to 50 to 55 mm Hg is based on the concept that the lower limit of autoregulation for cerebral blood flow is at this range (54). Because reduced arterial pressure may result in reduced flow to major organs, induced hypotension should be used cautiously, if at all, in patients with cardiovascular disease, cerebrovascular disease, renal dysfunction, or hepatic dysfunction.

Deliberate mild hypothermia, i.e., the lowering of body temperature to 30–32°C has been used to decrease metabolic oxygen demand in the Jehovah's Witness patient requiring an operative procedure where significant blood loss was expected (43,55). Hypothermia produces a significant reduction in oxygen consumption (56). The decrease in oxygen consumption is approximately 6% for every 1°C decrease in temperature (57). Other physiologic changes associated with hypothermia include an increase in oxygen solubility in plasma (58), an increase in blood viscosity (59), and an increase in peripheral vascular resistance that may contribute to a decrease in cardiac output (60). Deliberate hypothermia is best accompanied by hemodilution to avoid increasing viscosity and thus depressing cardiac output.

A target core temperature of 30–32°C is typically chosen because at this temperature arrhythmias do not usually occur (61) and yet the temperature is low enough to significantly decrease oxygen consumption. Surface cooling is adequate to produce mild hypothermia, and this can be accomplished with the use of a recirculating cooling blanket, of an operating room temperature between 18 and 20°C, and of an infusion of intravenous fluids at room temperature (55). Neuromuscular blocking agents and controlled ventilation should be used with this technique because voluntary muscle movement, spontaneous respiration, and shivering all increase oxygen consumption (62).

Many of the reports describing anesthesia in Jehovah's Witnesses for procedures where significant blood loss was expected employed hemodilution (43,55,63–65). Hemodilution reduces blood viscosity due to the decrease in hematocrit, a decreased tendency toward rouleaux formation, and decreased viscosity of the diluent (66). Associated with the hemodilution is an increased cardiac output and increased microcirculatory flow (66,67). Intraopera-

Table 2. Calculations for Autologous Blood Volume Withdrawal in Normovolemic Hemodilution

$$\text{Blood volume to remove} = \frac{{}^{*}\text{Hct}_\text{I} - \text{Hct}_\text{D}}{\frac{1}{2}(\text{Hct}_\text{I} + \text{Hct}_\text{D})} \times \text{EBV}$$

*Hct to be expressed as a decimal fraction; EBV = estimated blood volume; Hct_D = desired hematocrit after blood withdrawal; Hct_I = initial hematocrit.

tively, the blood lost contains fewer red cells per unit volume resulting in decreased loss of red cells.

Although the hemodilution reduces the reserve oxygen-carrying capacity of blood secondary to a reduced hemoglobin, cellular oxygen is maintained by decreased blood viscosity, increased dissolved oxygen-carrying capacity, and aided by mild hypothermia with subsequent decreased oxygen consumption (68). With the availability of oxygen minimized, however, it is imperative that there be close intraoperative monitoring of volume status, hematocrit, and tissue perfusion, which is reflected by the base deficit or serum lactate (43,55).

Moderate normovolemic hemodilution is considered to be a hematocrit of 20–25%, whereas severe hemodilution is below 20% (69). The amount of blood to be initially withdrawn is determined by a set of calculations illustrated in Table 2 (70).

With the Jehovah's Witness patient, it must be remembered that they typically require a continuous system of blood withdrawal and reinfusion. Use of a Haemonetics 30 blood cell processor to collect and reinfuse the blood and colloid or crystalloid at variable rates depending on surgical blood loss has been described (71). Simpler methods have also been described, including collection of blood from a central or peripheral vein into a bag containing a preservative and connected by a Y connector to either a bag of crystalloid or colloid that is infusing into another vein, thus creating a continuous circuit (43). If crystalloid is to replace the blood withdrawn, it should be 2–3 mL for each milliliter of blood removed (69). If it is colloid, it should be reinfused on a milliliter for milliliter basis (55).

Some controversy is present on whether to use crystalloid or colloid for hemodilution. Critics of colloid hemodilution predict prolonged anemia and hypervolemia postoperatively because of difficulty in removing the colloid by diuresis (72). Critics of crystalloid predict lower hematocrits with the initial hemodilution and marked edema intraoperatively (55). Concern for development of a coagulopathy is present when large volumes of hydroxyethyl starch (HES) are infused. There is a case report in the literature describing a severe coagulopathy after volume replacement with HES in a Jehovah's Witness (73). Synthetic macromolecular colloids have been reported to cause hemostatic defects by three possible mechanisms (74), although the clinical significance is not yet well defined (75). These mechanisms include 1) accelerated conversion of fibrinogen to fibrin that causes a less stable thrombus; 2) the macromolecules induce an acquired von Willebrand's syndrome; 3) macromolecules may coat circulating platelets causing a qualitative platelet function defect. HES has been used safely as a volume expander in amounts up to 1.5 g/kg normal body weight for intraoperative and the first 24-hr postoperative period (74,76). In the case report mentioned, the patient received 2.7 g/kg intraoperatively and the first 24-hr postoperative period.

Normovolemic hemodilution is one method of autotransfusion. The blood is collected immediately before the operative procedure with the majority reinfused after most of the surgical blood loss has occurred. Again, Jehovah's Witnesses typically require a continuous circuit of blood collection and retransfusion. Another form of autotransfusion that has been described for the Jehovah's Witness patient is intraoperative blood salvage from the surgical field and retransfusion with the use of the cell-saver (77,78). The cell-saver, for most Jehovah's Witnesses, appears to satisfy the requirement of a continuous circuit.

Desmopressin (DDAVP) has recently been suggested for use in the Jehovah's Witness patient to reduce intraoperative blood loss by increasing coagulability of blood (79). DDAVP, which increases plasma levels of factor VIII activity, has thus been used to reduce bleeding after cardiac surgery (80) and to reduce bleeding in patients undergoing Harrington rod insertion, 0.3 μ/kg usually being given intravenously over 20 min (81). DDAVP may, therefore, have a place in the perioperative management of the Jehovah's Witness patient.

Postoperative Management

Intravenous iron dextran has been used to optimize hemoglobin levels in Jehovah's Witness patients postoperatively (82,83). In addition, two reports (63,82) have described continuation of or institution of mild hypothermia and hemodilution in the postoperative management of severely anemic Jehovah's Witness patients.

Conclusion

Jehovah's Witnesses refuse blood or blood products on the basis of their religious beliefs. The decisions involved in how or even whether to care for a patient refusing necessary blood transfusion have to be made by each individual physician. These decisions should be guided by their knowledge, their own moral and ethical beliefs, and with regard to the convictions of their patient. This study has provided a review of the religious background of the Jehovah's Witnesses, the ethical issues and conflicts in caring for these patients, the significant past legal decisions rendered concerning this group, and how to proceed with anesthesia care when one elects to do so under the limits imposed by the patient's religious beliefs.

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References

1. Weinberger M, Tierney WM, Greene JY, Studdard PA. The development of physician norms in the United States: the treatment of Jehovah's Witness patients. Soc Sci Med 1982; 16:1719–23.
2. Tierney WM, Weinberger M, Greene JY, Studdard PA. Jehovah's Witnesses and blood transfusion: physician's attitudes and legal precedents. South Med J 1984;77:473–8.
3. Cole M. Jehovah's Witnesses. New York: Vantage Press, 1955:1–3.
4. Harrison BG. Visions of Glory: A History and Memory of Jehovah's Witnesses. New York: Simon and Schuster, 1978: 1–6.
5. Jehovah's Witnesses and the question of blood (pamphlet). New York: Watchtower and Bible Tract Society of New York, Inc., 1977.
6. Jansen AR. Blood transfusion and Jehovah's Witnesses. Crit Care Clin 1986;2:91–100.
7. Gardner B, Bivona J, Alfonso A. Major surgery in Jehovah's Witnesses. NY State J Med 1976;76:765–6.
8. Sandak LR. Suicide and the compulsion of lifesaving medical procedures: an analysis of the refusal of treatment cases. Brooklyn Law Rev 1978;44:285–316.
9. Studdard PA, Greene JY. Jehovah's Witnesses and blood transfusion. Toward the resolution of a conflict of conscience. Alabama J Med Sci 1986;23:454–9.
10. Dixon JL, Smalley MG. Jehovah's Witnesses. The surgical/ethical challenge. JAMA 1981;246:2471–2.
11. Dornette WHL. Jehovah's Witnesses and blood transfusion: the horns of a dilemma. Anesth Analg 1973;52:272–8.
12. Prince v. Commonwealth of Massachusetts, 321 U.S. 158 (1944).
13. Morrison v. State, 252 S.W. 97 (1952).
14. State v. Perricone, 181 A. 2d. 751 (1962).
15. Jehovah's Witnesses in State of Washington v. King County Hospital, 278 F. Supp 488 (1967).
16. Hudson v. Supreme Court of Washington, 126 P. 2d. 765 (1942).
17. Sampson v. Taylor, 29 N.Y. 2d. 900 (1972).
18. re Green, 292 A. 2d. 387 (1972).
19. Roe v. Wade, 93 S. Ct. 705 (1973).
20. Jefferson v. Griffin Spalding County Hospital Authority, 274 S.E. 2d. 457 (1981).
21. Taft v. Taft, 446 N.E. 2d. 395 (1983).
22. Anderson GR. Medicine vs. religion. The case of Jehovah's Witnesses. Health Soc Work 1983;8:31–8.
23. Schloendorff v. Society of New York Hospital, 105 N.E. 92 (1914).
24. Superintendent of Belchertown v. Saikewicz, 370 N.E. 2d. 417 (1977).
25. Erickson v. Dilgard, 252 N.Y.S. 2d. 705 (1962).
26. Aste v. Brooks, 205 N.E. 2d. 435 (1965).
27. In re Estate of Osborne, 294 A. 2d. 372 (1972).
28. United States v. George, 239 F.S. 752 (1965).
29. Commissioner of Corrections v. Myers, 399 N.E. 2d. 452 (1979).
30. Application of the President and Directors of Georgetown College, 331 F. 2d. 1000 (1964).
31. Luka v. Lowrie, 136 N.W. 1106 (1912).
32. Collins v. Davis, 254 N.Y.S. 2d. 666 (1964).
33. John F. Kennedy Memorial Hospital v. Heston, 279 A. 2d. 670 (1971).
34. Holmes v. Silver Cross Hospital, 340 F.Supp. 125 (1972).
35. Macklin R. The inner workings of an ethics committee: latest battle over Jehovah's Witnesses. Hastings Center Report 1988; 18:15–20.
36. Corno AF, Laks H, Stevenson LW, Clark S, Drinkwater DC. Heart transplantation in a Jehovah's Witness. J Heart Transplant 1986;5:175–7.
37. Ott DA, Cooley DA. Cardiovascular surgery in Jehovah's Witnesses. JAMA 1977;238:1256–8.
38. Henderson AM, Maryniak JK, Simpson JC. Cardiac surgery in Jehovah's Witnesses. A review of 36 cases. Anaesthesia 1986; 41:748–53.
39. Bonnett CA, Lapin R, Couyanan GB. Total hip replacements in Jehovah's Witnesses. Orth Rev 1987;16:92–6.
40. Nelson CL, Bowen WS. Total hip arthroplasty in Jehovah's Witnesses without blood transfusion. J Bone Joint Surg 1986; 68:350–3.
41. Bonakdar MI, Eckhous AW, Bacher BJ, Tabbilos RH, Peisner DB. Major gynecologic and obstetric surgery in Jehovah's Witnesses. Obstet Gynecol 1982;60:587–90.
42. Smith EB. Surgery in Jehovah's Witnesses. J Natl Med Assoc 1986;78:668–73.
43. Schaller RT, Shaller J, Morgan A, Furman EB. Hemodilution anesthesia: a valuable aid to major cancer surgery in children. Am J Surg 1983;146:79–83.
44. Clarke JMF. Surgery in Jehovah's Witnesses. Br J Hosp Med 1982;27:497–500.
45. Beausoleil v. Providential Sisters of Charity, 53 DLR 2d 65 (1964).
46. Medicolegal Forms With Legal Analysis. Chicago: American Medical Association, 1976:83.
47. Gardner B, Bivona J, Alfonso A, Herbsman HH. Major surgery in Jehovah's Witnesses. NY State J Med 1975;765–7.
48. Fatteh MM. Jehovah's Witnesses, how can we help them? J Med Assoc Ga 1980;69:977–9.
49. Herbsman H. Treating the Jehovah's Witness. Emerg Med Clin North Am 1980;12:73–6.
50. Sacks DA, Koppes RH. Blood transfusion and Jehovah's Witnesses: medical and legal issues in obstetrics and gynecology. Am J Obstet Gynecol 1986;483–6.
51. Oneson R, Douglas DK, Mintz PD. Jehovah's Witnesses and autologous transfusion. Transfusion 1985;25:179.

52. Vazeery AK, Lunde O. Controlled hypotension in hip joint surgery. Arch Orthop Scand 1979;50:433–7.

53. Thompson GE, Miller RD, Stevens WC. Hypotensive anesthesia for total hip arthroplasty: a study of blood loss and organ function (brain, heart, liver, kidney). Anesthesiology 1978; 48:91–6.

54. Harp JR, Wollman H. Cerebral metabolic effects of hyperventilation and deliberate hypotension. Br J Anaesth 1975;45: 256–8.

55. Adzick NS, deLorimier AA, Harrison MR, Glick PL, Fisher DM. Major childhood tumor resection using normovolemic hemodilution anesthesia and hetastarch. J Pediatr Surg 1985; 20:372–5.

56. Adolf EF. Oxygen consumption of hypothermic rats and acclimatization to cold. Am J Physiol 1950;161:359–73.

57. Michenfelder JD, Uihlein A, Daw EF, Theye RA. Moderate hypothermia in man: haemodynamic and metabolic effects. Br J Anaesth 1965;37:738–45.

58. Hedley-Whyte J, Laver MB. O_2 solubility in blood and temperature correction factors for pO_2. J Appl Physiol 1964;19:901–6.

59. Merill EW, Gilliland ER, Cokelet G. Rheology of human blood, near and at zero flow. Effects of temperature and hematocrit level. Biophys J 1963;3:199–213.

60. Rittenhouse EA, Ito DX, Mohri H, Merendino KA. Circulatory dynamics during surface induced hypothermia and after one hour of cardiac arrest. J Thorac Cardiovasc Surg 1971; 61:359–62.

61. Wynne NA, Fuller JA, Szekely P. Electrocardiographic changes in hypothermia. Br Heart J 1960;22:642–6.

62. Zwischenberger JB, Kirsch MM, Deckert RE, Arnold DK, Bartlett RH. Suppression of shivering decreases oxygen consumption and improves hemodynamic stability during postoperative rewarming. Ann Thorac Surg 1987;43:428–31.

63. Lichtenstein A, Eckhart WF, Swanson KJ, Vacanti CA, Zapol WM. Unplanned intraoperative and postoperative hemodilution: oxygen transport and consumption during severe anemia. Anesthesiology 1988;69:119–22.

64. Wong KC, Webster CR, Coleman SS, Dunn HK. Hemodilution and induced hypotension for insertion of a Harrington rod in a Jehovah's Witness patient. Clin Orth Rel Res 1980; 152:237–40.

65. Sandiford FM. Aortocoronary bypass in Jehovah's Witnesses: review of 46 patients. Am Surg 1976;42:17–22.

66. Messmer K. Hemodilution. Surg Clin North Am 1975; 55:659–78.

67. Messmer K, Sunder-Plassmann L, Kloevekorn WP, Holper K. Circulatory significance of hemodilution: rheologic changes and limitations. Adv Microcir 1972;4:1–77.

68. Messmer K, Sunder-Plassmann L, Jesch F, Goernandt L, Singowitz E, Kessler M. Oxygen supply to the tissues during limited normovolemic hemodilution. Res Exp Med 1973; 159:152–66.

69. Singler RC. Special techniques: deliberate hypotension, hypothermia and acute normovolemic hemodilution. In: Gregory GA, ed. Pediatric Anesthesia. New York: Churchill Livingstone, 1983:553–77.

70. Gross J. Estimating allowable blood loss: corrected for dilution. Anesthesiology 1983;58:277–80.

71. Lichtiger B, Dupuis JF, Seski J. Hemotherapy during surgery for Jehovah's Witnesses: a new method. Anesth Analg 1982; 61:618–9.

72. Laver MB, Buckley M. Extreme hemodilution in the surgical patient. In: Messmer K, ed. Hemodilution. Theoretical Basis and Clinical Application. International Symposium. Basel, Switzerland: S Karger, 1979:215–28.

73. Lockwood DNJ, Bullen C, Machin SJ. A severe coagulopathy following volume replacement with hydroxyethyl starch in a Jehovah's Witness. Anaesthesia 1988;43:391–3.

74. Macintyre E, Mackie IJ, Ho D, Tinker J, Bullen C, Machin SJ. The haemostatic effects of hydroxyethyl starch (HES) used as a volume expander. Intensive Care Med 1985;11:300–7.

75. Straus RG. Review of the effects of hydroxyethyl starch on the blood coagulation system. Transfusion 1981;21:299–302.

76. Shatney CH, Deepika K, Militello PR, Marjerus TC, Dawson RB. Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. Arch Surg 1983;118:804–9.

77. Calthorpe DAD, Finegan BA, Moriarty DC, Neligan MC. The use of the cell saver in a Jehovah's Witness undergoing major cardiac surgery—case report and review. Ir Med J 1983; 76:460–1.

78. Byrne MP. Abdominal aortic aneurysm surgery in the Jehovah's Witnesses: use of autotransfusion. Illinois Med J 1976; 150:87–9.

79. Stone DJ, DiFazio CA. DDAVP to reduce blood loss in Jehovah's Witnesses. Anesthesiology 1988;69:1028.

80. Salzman EW, Weinstein MJ, Weintraub RM, et al. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. N Engl J Med 1986;314:1402–6.

81. Kobrinsky NL, Letts RM, Patel LR, et al. I-desamino-8-D-arginine vasopressin (desmopressin) decreases operative blood loss in patients having Harrington Rod spinal fusion surgery. Ann Intern Med 1987;107:446–50.

82. Nearman HS, Eckhauser ML. Postoperative management of a severely anemic Jehovah's Witness. Crit Care Med 1983; 11:142–3.

83. Dudrick SJ, O'Donnell JJ, Raleigh DP, Matheny RG, Unkel SP. Rapid restoration of red blood cell mass in severely anemic surgical patients who refuse transfusion. Arch Surg 1985; 120:721–7.

Technical Communication

Isoflurane Uptake and Elimination Are Delayed by Absorption of Anesthetic by the Scimed Membrane Oxygenator

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STERN RC, WEISS CI, STEINBACH JH, EVERS AS. Isoflurane uptake and elimination are delayed by absorption of anesthetic by the Scimed membrane oxygenator. Anesth Analg 1989;69:657–62.

Although isoflurane is frequently used during hypothermic cardiopulmonary bypass (CPB), its pharmacokinetics in these circumstances have not been described for systems employing membrane oxygenators. The current study details isoflurane uptake and elimination in an ex vivo model of hypothermic CPB, which uses a Scimed membrane oxygenator. Isoflurane uptake and elimination by blood are markedly delayed by the membrane oxygenator in this system. This is because the oxygenator membrane absorbs large amounts of anesthetic; the Scimed oxygenator membrane has a capacity for anesthetic equivalent to ~17 L of blood. As isoflurane absorption by the oxygenator may also delay anesthetic uptake and elimination in patients during CPB, further studies in human subjects are needed to define the clinical significance of anesthetic absorption by the membrane oxygenator.

Key Words: ANESTHETICS, VOLATILE—isoflurane. ANESTHESIA, CARDIOVASCULAR—membrane oxygenators.

Volatile anesthetics are commonly used during hypothermic cardiopulmonary bypass (CPB) for their vasodilatory and anesthetic properties. It is particularly necessary to titrate blood anesthetic concentrations accurately in patients undergoing cardiothoracic surgery because of the increased susceptibility to anesthetic side effects. Several laboratories have begun to investigate the pharmacokinetics of anesthetic administration during CPB (1–3). Nussmeir et al. demonstrated that volatile anesthetic uptake and elimination were not significantly different from normothermic inhalational administration when agents were delivered via bubble oxygenators during hypothermic CPB (1,2). Anecdotally, we noted that the onset of isoflurane's hypotensive effect was markedly delayed when administered via a Scimed membrane oxygenator. Therefore, we postulated that the pharmacokinetics of isoflurane administration during CPB might be dependent upon oxygenator type. In order to investigate this hypothesis we initiated studies of uptake and elimination of volatile anesthetics in an ex vivo model system of CPB.

Methods

Materials

All chemicals used are commercially available and were obtained from the following companies: halothane—Ayerst Laboratories (New York, NY); isoflurane—Anaquest (Madison, WI); n-heptane (HPLC grade)—Fisher Scientific (Fair Lawn, NJ). The n-heptane used for gas chromatographic analysis was glass distilled before use to remove impurities.

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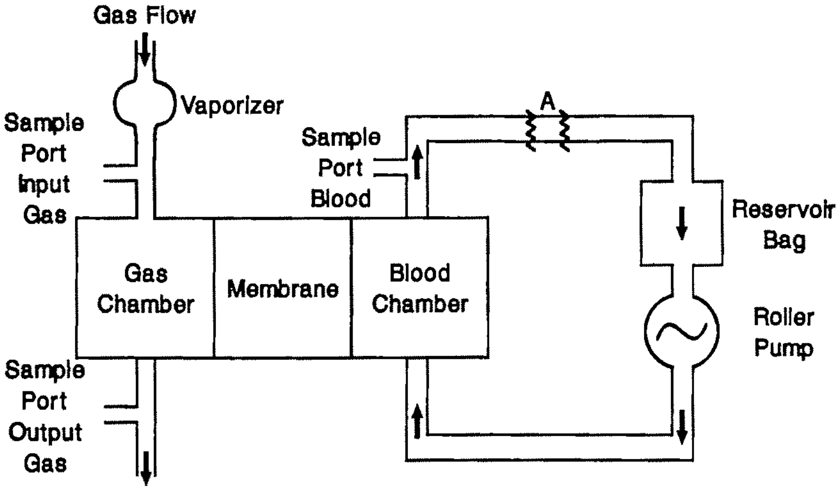

Figure 1. Diagram of the ex vivo cardiopulmonary bypass circuit. The three square compartments represent the functional chambers of the membrane oxygenator. Gas flow and blood flow proceed in the direction indicated by the arrows. In clinical use the CPB circuit is normally linked, in series, to the patient at point A.

The CPB circuit was constructed as diagrammed in Figure 1. The Scimed membrane oxygenator (Scimed Life Systems Inc., Minneapolis, MN, Model #1-35002A) was used for all kinetic studies. The blood circuit was constructed using 1.2 m of 9.4 cm diameter polyvinylchloride tubing, a 1300 mL reservoir bag, and 30 cm of 1.3 cm diameter silastic tubing for the roller pump boot. Blood flow was regulated using a precalibrated COBE-Stöckert Model #10 (COBE Laboratories, Inc., Lakewood, CO) roller pump. Gas flow was supplied through 0.6 m of 0.6 cm diameter polyvinylchoride tubing. Isoflurane in 100% oxygen was delivered using a Fortec (Ohmeda, Atlanta, GA) vaporizer.

Determination of Isoflurane Concentration in Blood

Anesthetic gas concentrations in blood were measured by an extensively modified technique based upon previously reported methods, which entails organic extraction of anesthetics from tissue and subsequent gas chromatographic (GC) analysis (4,5). Blood samples (1–2 mL) were obtained from the CPB circuit in gas-tight glass syringes. The blood was then added to preweighed tubes of ~3 mL of ice cold n-heptane containing halothane (1 mmol) as an internal standard. The tubes were then reweighed, mixed, and subsequently centrifuged to separate aqueous and organic phases. Exact volumes of blood and n-heptane were calculated by dividing their measured masses by the densities of heptane and blood. Preliminary experiments indicated that isoflurane (equilibrated with blood at 2 vol% concentration at 25°C) was completely extracted from blood under these conditions and that the halothane concentration in the n-heptane solution was unaffected by the extraction process. This was proven by reextracting the aqueous (blood) phase with 3 mL of neat n-heptane, which showed that < 1% of isoflurane and halothane remained in the aqueous phase.

Approximately 2 μL of the organic phase was used for GC analysis. A Hewlett Packard #5890 GC containing a DB-1 methylsilicone oil capillary column (15 m, 0.15 mm film thickness, 0.533 mm ID, from J & W Scientific, Folsom, CA) was used for sample analysis. Injections were made in the split mode (split flow ratio 20:1) with an injector temperature of 100°C. Runs were isothermal at 40°C using helium as a carrier gas at a flow rate of 1.0 mL/min. Signals were measured by flame ionization detection (280°C) using helium as a detector make-up gas (40 mL/min), and the ionization signals were recorded on a Hewlett Packard 3393A integrator for purposes of retention-time measurement and signal integration. In this system retention times of 1.96 and 2.21 min for isoflurane and halothane, respectively, were determined. To calculate isoflurane concentrations in the organic phase, the ratio of integration of the isoflurane and halothane peaks was calculated and corrected for the detector response ratio and the concentration of the internal standard (the detector response ratio for isoflurane to halothane responses was constant, 0.59, within the concentration range studied). To obtain the blood concentration of isoflurane, the organic phase concentration was multiplied by the ratio of n-heptane and blood volumes. Concentrations of isoflurane in blood as low as 0.06 mmol could be reproducibly and accurately measured (SD <10% of the mean for $n = 3$). Our method was ultimately validated in two ways: 1) by measuring the concentration of isoflurane in blood equilibrated with 2 vol% isoflurane gas at 37°C to yield a partition coefficient of 1.4 ± 0.07 SD ($n = 3$); 2) by measuring the saturating concentration of isoflurane in lactated Ringer's solution at 20°C (14.3 ± 0.6 mmol; $n = 4$). Both values are in close agreement with values reported in the literature (6,7), and the SD of measurement is small, thus confirming the reproducibility and accuracy of the technique. Sample determinations were repeated three times for each sample and the average value used for calculation of pharmacokinetic time points. All solutions containing volatile anesthetic were kept in gas-tight vials at 4°C.

Determination of Isoflurane Concentration in Gas

Isoflurane concentration in oxygen was measured by a modification of the method described by Heavner (8). Briefly, 5 mL gas samples were taken directly from the circuit in gas-tight glass syringes for GC analysis of isoflurane concentration. To ensure that precise volumes of gas were introduced to the column, a 250 μL loop on a manually activated Valco gas sampling valve was used for injection. A Hewlett Packard GC (Model #5890), containing a glass column packed with Porapaq Q, and a flame ionization detector was used for sample analysis. Isoflurane concentrations were determined by comparing signal integration measurements of samples to curves generated with standards prepared according to the ideal gas laws. Measurements of gas concentration were highly precise and accurate; therefore, only single determinations were made for gas samples at each time point.

Determination of Partition Coefficients

Blood/gas and membrane/gas partition coefficients ($\lambda_{B/G}$ and $\lambda_{M/G}$, respectively) for isoflurane were measured for blood used in the CPB circuit and for the Scimed membrane oxygenator. Determinations were made by adding a known volume of gas containing a measured concentration of isoflurane to a 100 mL gas-tight syringe containing a premeasured amount of either oxygenator membrane or blood. After allowing 5 min for mixing, isoflurane gas concentrations were measured using the GC method described above. Additional experiments indicated that longer equilibration periods (30 min) did not change the measured gas concentration. Partition coefficients were calculated using the principle of conservation of mass. By subtracting the amount of isoflurane measured in the gas after equilibration from the amount of isoflurane added before mixing and dividing the difference by the volume of membrane or blood, the concentration of isoflurane in membrane or blood was determined. Membrane volume was calculated by dividing the mass of the membrane by the density of the material reported by the manufacturer. The calculated isoflurane concentration in membrane or blood was divided by the measured concentration of isoflurane in gas after equilibration to give the $\lambda_{M/G}$ or $\lambda_{B/G}$. The $\lambda_{B/G}$ of saline-diluted blood at 25°C (i.e., the blood used in the oxygenator circuit) was determined using this method, yielding the same values (1.47 ± 0.1 SE, $n = 4$) reported by others using similar methodology (1,2). Partition coefficients are reported as the average of three separate determinations ± SE. Measurements were made at 25°C.

Determination of Uptake and Elimination Kinetics of Isoflurane in Blood

The CPB circuit was assembled as shown in Figure 1. A mixture of lactated Ringer's solution, 10,000 units of heparin, and recently outdated whole blood was added to the circuit to give a hematocrit of approximately 25% and a volume of 1100 mL. The circuit was "de-aired" and equilibrated at predetermined rates of blood flow (Q, in L/min) and gas flow (F, in L/min). Isoflurane delivery at ~2 vol% concentration was then initiated. Blood and gas samples were collected at predetermined time intervals and processed for analysis as described above. Experiments were repeated in the same membrane oxygenator for different values of Q and F after washout of isoflurane was completed. Complete washout was confirmed by measuring <0.01 vol% isoflurane concentrations in gas exiting the oxygenator. Experiments were performed three times in three separate membrane oxygenator systems, except for measurements made at $F = 3$, $Q = 1.5$, which were performed twice. The range of F and Q values studied spanned the range of clinically used settings for this oxygenator. Pharmacokinetic results are expressed as the ratio of the measured concentration to the maximal potential concentration (C/C_{max}) as a function of time. Maximal concentrations of isoflurane (C_{max}) for uptake were calculated by multiplying the measured isoflurane blood/gas partition coefficient by the measured isoflurane concentration in delivered gas.

Elimination kinetics were measured at $F = 3$, $Q = 3$. Samples were taken at specific times after isoflurane delivery was terminated. Samples taken just before the termination of isoflurane administration were used as a measure of C_{max} for elimination. Results are expressed as C/C_{max} as a function of time. Experiments were performed three times using three different membrane oxygenators.

Determination of Anesthetic Uptake by the Membrane Oxygenator

The CPB circuit was assembled as described in Figure 1, with the exception that the compartment for blood was left empty and the blood tubing clamped immediately proximal and distal to the oxygenator blood chamber. Oxygen was allowed to flow through the system at either 1.5, 3, or 6 L/min. Delivery of ~2 vol% isoflurane was then initiated, and samples of delivered and exit gas obtained at specific time intervals. Experiments for F = 3 were repeated in three different membrane oxygenators. Experiments for F = 1.5 and 6 were performed in a single oxygenator. A single experiment was done (for F = 3) in which the same protocol was followed with the exception that the blood circuit was filled with blood and circulating at a rate of 3 L/min. Washout of isoflurane between experiments was confirmed by measuring <0.01 vol% isoflurane in exit gas. Results are expressed as the ratio of exit to inflow gas concentration (Ce/Ci) as a function of time.

Statistical Methods

C/C_{max} time points for uptake and elimination of isoflurane by blood were calculated as the mean ± SE of three separate experiments, except for experiments in which F = 3, Q = 1.5. In this case time points were calculated as the mean ± range ($n = 2$). Uptake and elimination data were fit to curves using a nonlinear least squares software program (NFITS—edited by Dr. C.J. Lingle). The data were fit by uniexponential functions which describe uptake and elimination in our system; $C/C_{max} = 1 - e^{-kt}$ for uptake and $C/C_{max} = e^{-kt}$ for elimination, where t is time and k is the rate constant. Data are expressed in terms of time constants (τ), where $\tau = 1/k$, to make kinetic comparisons more comprehensible. Time constants are reported as the mean ± SE. Statistical comparisons were performed using a STATA software program (Computing Resource Center, Los Angeles, CA). Time constants were compared using a one-way analysis of variance followed by a Bonferroni multiple comparison test of the means at a significance level of 0.05.

Ce/Ci time points were calculated as the mean ± SD ($n = 3$) of three separate experiments for F = 3. All other Ce/Ci time points were the result of single determinations.

Results

In initial studies we measured blood concentrations of isoflurane as a function of time during continuous delivery of isoflurane via the Scimed oxygenator to the CPB circuit (see Figure 2). Equilibration of blood with input gas occurred relatively quickly at a gas flow (F) of 6 L/min, and more slowly at less rapid gas flows. Isoflurane uptake by blood was found to be an exponential function of time. Uptake curves were closely fit (confidence limits >90%) by a uniexponential function for a single compartment dilution with a constant drug delivery, $C/C_{max} = 1 - e^{-kt}$ (where $k = 1/\tau$). Time constants for uptake were 15 ± 1.2 for F = 1.5, 5.4 ± 0.2 for F = 3, and 3.1 ± 0.3 for F = 6 (all units in min ± SE), and were all significantly different at $P < 0.05$. Changing blood flow (Q) from 3.0 to 1.5 L/min did not significantly alter the rate of uptake; the time constants were 5.1 ± 0.2 for Q = 1.5 and 5.4 ± 0.2 for Q = 3. This indicates that isoflurane uptake by blood is highly dependent upon the rate of gas delivery but relatively uninfluenced by the rate of blood flow in this system.

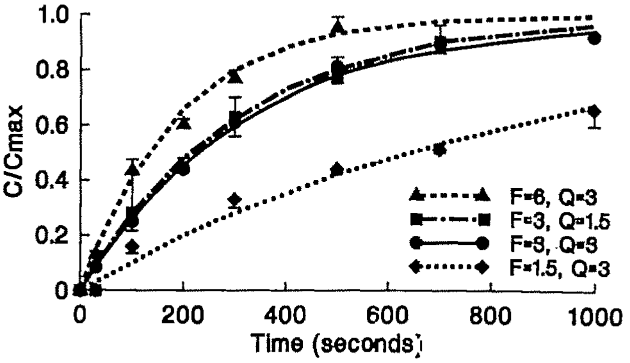

Figure 2. Isoflurane uptake by blood as a function of time. Blood isoflurane concentrations (C) were measured after initiating administration of 2 vol% isoflurane at different rates of gas flow (F in L/min) and blood flow (Q in L/min). Concentration measurements were normalized to the maximum isoflurane concentration achievable in blood for delivered concentrations of isoflurane in gas (C_{max}). Curves were fit by a nonlinear least squares method using an exponential function for a one compartment dilution with a constant drug delivery rate, $C/C_{max} = 1 - e^{-kt}$. Data points and error bars for all experiments performed at Q = 3 represent the mean ± SE of the results of three separate experiments. Data points and error bars for F = 3, Q = 1.5 represent the mean ± range of two separate experiments.

Subsequent experiments examined the elimination of isoflurane from blood after discontinuation of isoflurane delivery at a gas flow of 3 L/min. As shown in Figure 3, isoflurane was slowly eliminated from blood with a $t_{1/2}$ of elimination of ~5 min. Elimination curves were closely fit (confidence limits > 90%) by a uniexponential function for elimination, $C/C_{max} = e^{-kt}$ (where $k = 1/\tau$). The time constant of elimination of isoflurane from blood was 7.0 ± 1.0 min. The time constants for uptake and elimination at F = 3, Q = 3, did not differ significantly from each other ($P > 0.05$).

To determine the effect of anesthetic absorption by the membrane oxygenator on isoflurane pharmacoki-

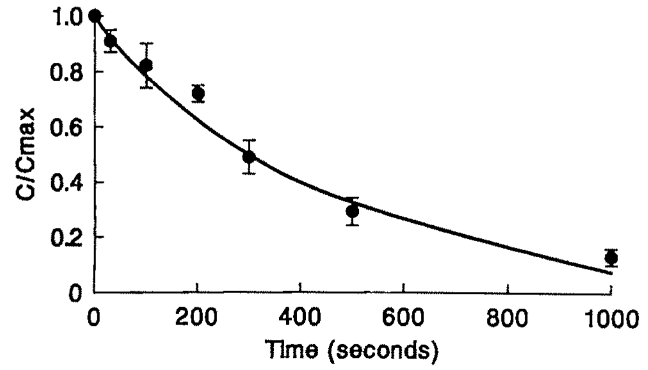

Figure 3. Elimination of isoflurane from blood as a function of time. Blood concentrations of isoflurane (C) were measured after uptake experiments at F = 3, Q = 3 were completed. Concentration measurements were normalized to the concentration of isoflurane measured at time = 0 (C_{max}). Curves were fit to the data by a nonlinear least squares method using a declining exponential function, $C/C_{max} = e^{-kt}$. Data points and error bars represent the mean ± the SE of the results of three separate experiments.

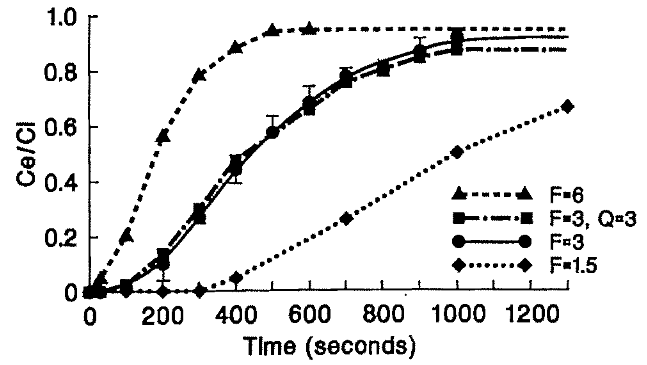

Figure 4. Isoflurane absorption by the oxygenator as a function of time. Isoflurane concentrations in gas exiting the oxygenator were measured after initiating delivery of 2 vol% of isoflurane at specific rates of total gas flow delivery. All data were normalized to isoflurane concentration in delivered gas and therefore expressed as a ratio, Ce/Ci (gas concentration in exit gas/delivered gas). The dash/dotted line represents data from experiments in which the blood circuit was filled with blood circulating at a rate of 3 L/min. All other curves represent data from experiments in which the blood circuit was empty, and the blood circuit tubing clamped just distal to the inlet and outlet of the blood chamber. Data points and error bars for F = 3 represent the mean ± SD of the results of three separate experiments. Data points for all other curves are derived from single experiments. All curves were drawn using a Harvard Graphics, version 2.0, software program.

netics, we examined uptake of anesthetic in the presence and absence of the circulating blood (see Figure 4). In these experiments serial measurements of anesthetic gas concentration in inflow and outflow oxygenator gas were made. The rate of rise of output gas concentration was found to be a function of the rate of gas delivery; output concentrations more rapidly approached input concentrations at high gas flows. Subsequent measurements of input and output gas concentration were made with circulating blood present in the CPB circuit. As shown in Figure 4, the presence of blood had an insignificant effect on the rate of equilibration of output gas with input gas. Hence the oxygenator, not blood, was shown to be the major site of isoflurane absorption.

In order to quantitate the effect of isoflurane absorption by the oxygenator on the kinetics of isoflurane uptake by blood, the amount of anesthetic absorbed as gas traversed the oxygenator was calculated and compared to the amount of anesthetic required to saturate blood at delivered concentrations of isoflurane gas. Anesthetic absorbed per unit time was calculated by integrating the difference in the amounts of isoflurane in input and output gas as a function of time. Calculations of absorption were adjusted for the transit time of gas through the oxygenator by reassigning the initial time point for integration as the transit time. This modification in the calculation was made in order to maximally take into account the lag in the measurement of isoflurane in exit gas that is created by the distance the input gas must traverse within the oxygenator before being measured in exit gas. Transit times were calculated by dividing the volume of gas space in the oxygenator (~800 mL) by the gas flow rate. Transit times for F = 1.5, 3, and 6 were 32, 16, and 8 sec, respectively. We then calculated the amount of time it would take blood to equilibrate with delivered concentrations of isoflurane if all isoflurane absorbed were absorbed by blood. This was done by dividing the amount of anesthetic absorbed per unit time by the capacity of blood for isoflurane ($\lambda_{B/G}$ × blood volume × Ci). Predicted equilibrium times (23, 46, and 92 sec for F = 6, 3, and 1.5, respectively) were an order of magnitude smaller than experimentally measured times of equilibration (approximately 500, 700, and > 1000 sec for F = 6, 3, and 1.5). These data indicate that the Scimed oxygenator does not directly transfer delivered anesthetic into blood but rather acts as a reservoir for isoflurane which slows the rate of rise of blood anesthetic concentrations.

To prove directly that the oxygenator membrane was the site of anesthetic absorption we dissected the membrane from the oxygenator and measured its capacity for isoflurane. The capacity of the oxygenator was calculated by multiplying the $\lambda_{M/G}$ of the oxygenator (26.3 ± 1.2 SE) by the volume of the oxygenator membrane (~900 mL). In order to relate the capacity of the oxygenator to some physiologic parameter, we divided the capacity of the oxygenator for isoflurane by the isoflurane partition coefficient of blood ($\lambda_{B/G}$ ~1.4). In this way we determined that the oxygenator has a capacity for isoflurane equivalent to ~17 L of blood.

Discussion

In an ex vivo model of CPB, we have found that isoflurane uptake and elimination by blood are delayed by absorption of anesthetic by the Scimed membrane oxygenator. Our experiments show that large amounts of anesthetic are absorbed by the oxygenator, and that the majority of absorbed anesthetic is not transferred directly into blood. Membrane uptake of anesthetic was calculated to delay equilibration between blood and delivered gas by more than an order of magnitude. Another consequence of anesthetic absorption by the oxygenator is that the rate of blood flow in the pump circuit (within the range commonly used during CPB) becomes an insignificant determinant of isoflurane uptake kinetics. This is because anesthetic uptake by the membrane is the rate-limiting step for the increase of anesthetic concentrations in blood. Based on these studies it is concluded that the Scimed membrane acts as a reservoir for anesthetic, one that serves to slow both isoflurane uptake and elimination by blood.

The Scimed membrane oxygenator delays isoflurane uptake and elimination ex vivo by virtue of its high affinity for anesthetic and the large volume of its membrane. The behavior of other membrane oxygenators may be distinctly different because they contain membranes composed of different types and amounts of plastic. Therefore, conclusions drawn from data obtained in studies of the Scimed oxygenator should not be directly generalized to other membrane oxygenator types.

The pharmacokinetics of volatile anesthetic administration via bubble oxygenators and the Scimed oxygenator might also be expected to be different. Unlike membrane oxygenators in which drug and gas exchange occurs through a synthetic membrane, gas exchange proceeds directly in bubble oxygenators via a gas-blood interface (bubbles). Hence one would expect that bubble oxygenators would not delay anesthetic uptake and elimination. Consistent with this hypothesis is the finding that uptake and elimination of volatile anesthetics in human subjects during hypothermic CPB using bubble oxygenators are very similar to uptake and elimination during conventional inhalational administration (1,2).

Unlike bubble oxygenators, long delays in isoflurane uptake and elimination during clinical use of the Scimed membrane oxygenator may result from the additive effects of anesthetic absorption by the membrane and patient tissues. If the delay in anesthetic uptake and elimination by the membrane oxygenator is clinically significant, this could exacerbate problems associated with the administration of volatile anesthetics during CPB (e.g., unanticipated delays in elimination of volatile anesthetic could result in the presence of unwanted cardiac depression during separation from CPB). Clearly any clinical inferences from our ex vivo data are speculative, not conclusive; further studies in human subjects must be done to determine the clinical effect of the Scimed membrane oxygenator on volatile anesthetics pharmacokinetics during CPB.

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References

1. Nussmeir NA, Cohen NH, Moskowitz GJ, et al. Washin and washout of three volatile anesthetics concurrently administered during cardiopulmonary bypass. Anesthesiology 1988;69:A84.
2. Nussmeir NA, Lambert ML, Moskowitz GJ, et al. Washin and washout of isoflurane during cardiopulmonary bypass. Anesth Analg 1988;67:S159.
3. Rosen D, Rosen K, Davidson B, Broadman L. Fentanyl uptake by the Scimed membrane oxygenator. J Cardiothorac Anesth 1988;2:619–26.
4. Bazil CW, Raux ME, Yudell S, Minneman KP. Equilibration of halothane with brain tissue in vitro: Comparison to brain concentrations during anesthesia. J Neurochem 1987;49:952–8.
5. Saraiva RA, Willis BA, Steward A, Lunn JN, Mapleson WW. Halothane solubility in human blood. Br J Anaesth 1977;49:115–9.
6. Roth SH, Miller KW. Molecular and Cellular Mechanism of Anesthetics. 1st ed. New York: Plenum Publishing Co, 1986:468.
7. Eger RR, Eger EI II. Effect of temperature and age on the solubility of enflurane, halothane, isoflurane, and methoxyflurane in human blood. Anesth Analg 1985;64:640–2.
8. Heavner JE, Friedhoff J, Haschke R. Gas chromatographic assay of volatile anesthetics: Some problems and a solution. Anesthesiology 1976;45:654–5.

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Clinical Reports

Esmolol in the Management of Epinephrine- and Cocaine-Induced Cardiovascular Toxicity

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Key Words: ANESTHETICS, LOCAL—cocaine.

Many treatments have been suggested for management of life-threatening hypertension, tachycardia, and myocardial ischemia associated with hyperadrenergic states (1–6). The availability of the short-acting β_1-selective blocking drug esmolol has allowed more precise control of catecholamine surges without fear of overtreatment. We report a case in which esmolol was beneficial in the perioperative management of epinephrine- and cocaine-induced cardiovascular toxicity. To our knowledge, this case represents the first reported use of this agent in this situation.

Case Report

A 64-year-old obese man presented with difficulty breathing because of bilateral nasal polyps. There was a 15-year history of asthma and allergy to aspirin. In addition, there was a history of long-standing atrial fibrillation dating back to a myocardial infarction 20 years previously and of stable exertional angina and hypothyroidism. Physical examination was unremarkable with the exception of an irregular pulse of 90 beats/min and blood pressure of 144/90 mm Hg. Electrocardiogram (ECG) revealed an old septal myocardial infarction and atrial fibrillation with a ventricular rate of 88 beats/min. Serum levels of electrolytes, blood urea nitrogen, and creatinine, as well as the hematocrit, were within normal limits.

The patient was premedicated with meperidine (50 mg), hydroxyzine (25 mg), and atropine (0.3 mg) intramuscularly in addition to his usual medications of digoxin, theophylline, and levothyroxine plus use of metaproterenol and beclomethasone inhalers. In the operating room, blood pressure was 155/100 mm Hg and pulse 116 beats/min. Electrocardiogram confirmed that the patient was in atrial fibrillation. Oxygen was given through an oral cannula at 2 L/min. Fentanyl (75 μg) and midazolam (2.5 mg) were given in small increments intravenously to achieve sedation, bringing the heart rate down to 90 beats/min and the blood pressure down to 140/80 mm Hg.

In preparation for nasal polypectomies, 10 mL of 1% lidocaine with epinephrine 1:200,000 was injected into the nasal mucosa. Shortly afterward, cocaine (160 mg) was applied topically to the nasal mucosa. Within minutes, the patient's heart rate increased to 150 beats/min and blood pressure to 180/112 mm Hg. ST-segment depression appeared on the precordial leads; the patient denied chest pain or dyspnea. Two doses of digoxin, each 0.125 mg IV, failed to decrease the heart rate over the next 15 min. Nitroglycerin paste (2.5 cm) was applied on the skin over the precordium. Eight minutes later, esmolol (20 mg) was given in an intravenous bolus followed by infusion of a 1% solution at a rate sufficient to keep the heart rate under 100 beats/min. Blood pressure, heart rate, and ST-segment changes returned to preoperative levels within minutes of beginning the esmolol infusion, and surgery was completed uneventfully.

The esmolol infusion was continued in the recovery room at ever decreasing rates until it was discontinued after 150 min. There was no evidence of bronchospasm. Postoperative ECG was unchanged. The patient was discharged from the hospital the next day after an uneventful recovery.

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Discussion

The administration of cocaine to the nasal mucosa was the unfortunate result of poor communication between surgeon and anesthesiologist. The hyperadrenergic state that developed in this patient in all probability represents the response to both the epinephrine and topical cocaine administration. It is extremely unlikely that the effect of 50 μg of submucosally injected epinephrine alone could cause the cardiovascular effects that lasted for the hours during which the patient required treatment. On the other hand, the half-life of cocaine in the plasma after nasal administration is about 1 hr (7). Its biodegradation by plasma cholinesterases is also slower in elderly patients. Tachycardia, hypertension, and myocardial ischemia are well recognized as cardiovascular effects (8).

Beta-adrenergic blockade has been advocated in the management of cocaine toxicity because of its "strikingly specific antagonistic effects" (1). Others (2) report hypertension resulting from nonspecific beta-blockade in cocaine toxicity, presumably as the result of unopposed alpha-adrenergic stimulation. Labetolol, a combined alpha- and beta-antagonist, has been advocated as a solution (3,4). It has been suggested, however, that because of the more potent beta-blocking than alpha-blocking properties of labetolol, a possibility exists for "relatively unopposed alpha effect" (5). Alternatively, β_1-selective blockers have been advocated as a means of avoiding coronary arterial and peripheral vascular vasospasm due to unopposed alpha-adrenergic stimulation (9).

Esmolol is an ultrashort-acting β_1-selective adrenergic blocker with an elimination half-life of about 9 min (10). We found it was an attractive choice for the treatment of a cocaine-induced hyperadrenergic state for many reasons: 1) the patient's heart rate could be gradually reduced without fear of inducing sustained bradycardia; 2) the β_1-selective effects of esmolol made it a safer choice for a patient with reactive airways disease; 3) other available parenteral or oral beta-blocking agents act for several hours, whereas the effects of cocaine could be expected to start to wane over an hour or so; and 4) β_1-selective effects render hypertension or coronary artery spasm from unopposed alpha-adrenergic tone less of a risk than with nonselective beta-blocking drugs.

Surgeons and anesthesiologists should make every effort to avoid situations in which epinephrine and cocaine are used simultaneously. Should such a situation occur and a hyperadrenergic state result, intravenous esmolol has proved effective in managing the cardiovascular response. The experience in this case leads us to believe that intravenous esmolol would be equally effective in the emergency room management of cardiovascular responses to overdoses of "crack" or other forms of cocaine.

References

1. Rapport RT, Gay GR, Inaba DS. Propanolol: a specific antagonist to cocaine. Clin Toxicol 1977;10:265–71.
2. Ramoska E, Sacchetti AD. Propanol-induced hypertension in treatment of cocaine intoxication Ann Emerg Med 1985; 14:112–3.
3. Gay GR, Loper KA. Control of cocaine-induced hypertension with labetolol. Anesth Analg 1988;67:91–4.
4. Gay GR, Loper KA. The use of labetolol in the management of cocaine crisis. Ann Emerg Med 1988;17:282–3.
5. Bessen HA. Treatment of cocaine toxicity (letter). Ann Emerg Med 1987;16:922.
6. Nicholas E, Deutschman CS, Allo M. Use of esmolol in the intraoperative management of pheochromocytoma. Anesth Analg 1988;67:1114–7.
7. Ritchie JM, Greene NM. Local anesthetics. In: Gilman AS, Goodman LS, Rall TW, Murad F, eds. The pharmacological basis of therapeutics. 7th ed. New York: MacMillan Publishing, 1985:309–10.
8. Cregler LL, Mark H. Medical complications of cocaine abuse. New Engl J Med 1986;315:1495–500.
9. Deedwania PC, Carbajal E. Current perspectives in treatment of angina pectoris. Postgrad Med 1986;80:189–206.
10. Lui PL, Gugino LD, Covino BG. Esmolol for control of increases in heart rate and blood pressure during tracheal intubation after thiopentone and succinylcholine. Can Anaesth Soc J 1986;33:556–62.

Differential Effect of Prostaglandin E_1 and Sodium Nitroprusside on Intrapulmonary Shunt Fraction in a Cardiac Transplantation Patient

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Key Words: HORMONES, PROSTAGLANDIN E_1.

Many candidates for cardiac transplantation present with pulmonary hypertension, and determination of acceptability for transplantation depends upon differentiation of fixed and reactive components of pulmonary vascular resistance (PVR). Currently, sodium nitroprusside (SNP) is widely used to assess the degree of pharmacologic reversibility of elevated PVR. There is evidence to indicate, however, that SNP inhibits hypoxic vasoconstriction and may increase intrapulmonary shunt fraction (Q_S/Q_T) (1,2), responses which could be particularly deleterious in patients with limited cardiopulmonary reserve. Conversely, there are data to suggest that prostaglandin E_1 (PGE_1), a relatively selective pulmonary vasodilator, reduces PVR in patients with adult respiratory distress syndrome (ARDS) without affecting an already elevated Q_S/Q_T (3). More recent investigation, however, has produced conflicting results (4). How PGE_1 influences Q_S/Q_T in patients with cardiogenic pulmonary hypertension but normal gas exchange awaiting cardiac transplantation remains unclear. The following case report describes the use of PGE_1 in such a patient. It also documents the difference in Q_S/Q_T changes when SNP or PGE_1 were used to lower PVR immediately before operation.

Case Report

A 43-year-old man with an ischemic cardiomyopathy and NYHA class IV symptoms of angina and congestive heart failure (CHF) presented for cardiac transplantation. Previous cardiac history was notable for a myocardial infarction in the distant past with development of a left ventricular aneurysm which was resected 3 years before admission. Postoperatively, the patient continued to have angina and developed episodic CHF. Medical history was otherwise notable for a 30 pack-year (average of 1 pack a day for 30 years) smoking history.

The patient was initially admitted to the hospital 5 weeks before transplantation with recurrent CHF. After initial treatment and stabilization, a diagnostic right heart catheterization determined the baseline PVR to be 300 dyne·sec·cm^{-5}; this value fell to approximately 200 dyne·sec·cm^{-5} during SNP infusion. Q_S/Q_T was not measured. The patient remained hospitalized for management of persistent CHF until transplantation. Medications at the time of surgery included amrinone (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), furosemide (20 mg each morning), digoxin (0.25 mg each morning), and isosorbide dinitrate, which had been discontinued on the day of surgery and replaced with nitropaste. All oral medications had been administered 8 to 12 hr before surgery, as had a single 50-mg dose of captopril. Amrinone infusion was continued at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until institution of cardiopulmonary bypass.

In order to document continued pulmonary vascular suitability for transplantation, a second right heart catheterization was performed immediately before acceptance of the donor organ as part of a standard institutional protocol. After establishing venous and arterial access, the patient was sedated with intravenous midazolam (total dose 5 mg) and morphine (total dose 10 mg). Baseline arterial blood gas tensions while breathing room air were pH 7.39, Po_2 80 mm Hg, and Pco_2 37 mm Hg. The patient was then given face-mask oxygen (6 L of flow—approximate FI_{O_2} 0.4), which was not altered throughout the entire period of observation. A pulmonary arterial (PA) catheter capable of atrioventricular (AV) sequential pacing was placed percutaneously via the left internal jugular vein. Monitored hemodynamic variables included continuous systemic arterial, PA, and right atrial (RA) pressures, heart rate, and intermittent

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Table 1. Comparative Responses to Vasodilator Infusion of Sodium Nitroprusside (SNP) and PGE_1

	Baseline	SNP ($1.75\ \mu g \cdot kg^{-1} \cdot min^{-1}$)	SNP off	PGE_1 ($70\ ng \cdot kg^{-1} \cdot min^{-1}$)
HR (beats/min)	92	96	93	92
mPAP (mm Hg)	48	36	45	35
PCWP (mm Hg)	24	22	23	23
mAP (mm Hg)	80	72	82	68
RAP (mm Hg)	13	7	11	8
CO (L/min)	3.01	5.12	3.15	4.80
PVR ($dyne \cdot sec \cdot cm^{-5}$)	638	219	559	200
SVR ($dyne \cdot sec \cdot cm^{-5}$)	1781	1016	1803	1000
Pao_2 (mm Hg)	142	68	110	99
$Paco_2$ (mm Hg)	36	37	37	38
Pvo_2 (mm Hg)	39	50	42	49
Q_S/Q_T (%)	6	51	13	18

Hemodynamic, blood gas, and intrapulmonary shunt (Q_S/Q_T) data before and during infusion of sodium nitroprusside (SNP) or prostaglandin E_1 (PGE_1). HR: heart rate; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; mAP: mean systemic arterial pressure; RAP: right atrial pressure; CO: cardiac output; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; Q_S/Q_T: intrapulmonary shunt fraction—calculated as:

$$Q_S/Q_T = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_vO_2},$$

where: $C_cO_2 = (1.39 \times Hgb)\ S_AO_2 + (0.0031 + P_AO_2)$
$C_aO_2 = (1.39 \times Hgb)\ S_aO_2 + (0.0031 + P_aO_2)$
$C_vO_2 = (1.39 \times Hgb)\ S_vO_2 + (0.0031 + P_vO_2)$
P_AO_2—from alveolar gas equation.

measurements of thermodilution cardiac output (CO) and pulmonary capillary wedge pressure (PCWP). Arterial and venous blood analysis was performed with Instrumentation Laboratories' 1306 pH/blood gas analyzer and 482 Co-oximeter.

After a 10-min stabilization period, hemodynamic measurements were made and baseline arterial and mixed venous blood samples were obtained. Hemodynamic variables, blood gas data, calculated vascular resistances, and Q_S/Q_T are shown in Table 1. Nitroprusside was then infused incrementally through the PA catheter introducer (maximal dose $1.75\ \mu g \cdot kg^{-1} \cdot min^{-1}$) until PVR had been reduced to approximately 200 $dyne \cdot sec \cdot cm^{-5}$ (Table 1). Despite an increase in Pvo_2, arterial Po_2 decreased to 68 mm Hg from 142 mm Hg. SNP infusion was therefore discontinued and hemodynamic variables allowed to return to near baseline levels.

To determine if pulmonary vasodilation with another agent would more favorably maintain gas exchange, after a 15-min stabilization period (projected arrival time of the donor organ prevented waiting longer), PGE_1 was incrementally infused through the PA catheter introducer until PVR had been reduced to a similar level as that obtained with SNP (Table 1). The final PGE_1 dose was $70\ ng \cdot kg^{-1} \cdot min^{-1}$. Unlike SNP, PGE_1 did not dramatically alter either arterial Po_2 or Q_S/Q_T. Due to the favorable hemodynamic and respiratory responses, PGE_1 infusion was maintained during induction of anesthesia and continued throughout the entire perioperative period. Cardiac transplantation was successful, and the patient was discharged from the hospital on the 14th postoperative day.

Discussion

Prostaglandin E_1 is a monoenoic eicosinoid produced endogenously in small quantities by the cyclooxygenation of dihomo-γ-linolenic acid (5). The compound has antiinflammatory, antiplatelet, and cardiovascular effects and has been used extensively in pediatrics to maintain patency of the ductus arteriosus in patients with ductus-dependent congenital heart disease (5). In adults, PGE_1 has been used in the treatment of pulmonary hypertension from a variety of causes (6), left ventricular failure secondary to acute myocardial infarction (5), peripheral vascular disease (7), Raynaud's disease (8), and ARDS (3). PGE_1 also effectively reduces right ventricular afterload and improves pump function after mitral valve replacement or cardiac transplantation (9,10).

The relative selectivity of PGE_1 for the pulmonary circulation lies in the high degree of extraction/metabolism (approximately 80–85%) of the compound that occurs in pulmonary arterial blood during a single pass through the lungs (5). Systemic hypotension can, however, occur when large doses are administered.

Although studies in a hypoxic animal model indicate an increase in Q_S/Q_T during PGE_1 infusion (11), this does not appear to be true for normal human subjects (12). In critically ill patients with impaired gas exchange and elevated PVR, PGE_1 has been reported both not to change (3) and to increase (4) Q_S/Q_T. It has been our clinical impression that PGE_1 used intraoperatively to treat pulmonary hypertension does not alter Pao_2. The patient presented here is representative of many transplant candidates in that a long history of cigarette smoking imposes reduced pulmonary reserve on top of cardiac dysfunction. In such patients it is particularly necessary to maintain optimal oxygenation at all times, especially during induction of general anesthesia.

The ability of SNP to inhibit hypoxic vasoconstriction and increase Q_S/Q_T is well documented (1,2), and the decrease in this patient's Po_2 during SNP infusion was not unexpected. The magnitude of the decline, however, was greater than anticipated and thus prompted us to consider using another pulmonary vasodilator. It should be noted that Q_S/Q_T was calculated with a standard formula which is most accurate when an FI_{O_2} of 1.0 (i.e., while intubated) is assured (13). Based on published guidelines (14), we have assumed a continuous FI_{O_2} of 0.4 in calculating Q_S/Q_T in this patient. We have also assumed that minute ventilation remained relatively constant as evidenced by minimal change in Pco_2. Thus, while the relative changes in Q_S/Q_T produced by SNP and PGE_1 are apparent, the absolute values should probably be regarded as estimates.

Both SNP and PGE_1 were effective in demonstrating the reversibility of this patient's elevated PVR. In fact, both drugs, at the doses given, produced similar pulmonary and systemic vascular responses and increases in CO and Pvo_2. The only clear difference was a decrease in Pao_2 and an increase in calculated Q_S/Q_T during SNP infusion. In contrast, Prielipp et al. (15) found in a sheep model of noncardiogenic pulmonary hypertension that despite roughly similar reductions in right and left ventricular afterload, PGE_1 increased CO, Pvo_2, and Q_S/Q_T while SNP had no effect. The authors speculate that the potent venodilating action of SNP may have limited venous return and prevented an increase in CO. Increases in mixed venous Po_2 and CO have been shown independently to increase Q_S/Q_T (16). Thus the increase in Q_S/Q_T produced by PGE_1 and not by SNP in the sheep model of pulmonary hypertension may be the result of their differential effect on CO and Pvo_2.

Our findings suggest that PGE_1 may be a better alternative to SNP in the preoperative evaluation of patients for cardiac transplantation. Furthermore, PGE_1 may represent a valuable adjunct to optimizing cardiac function while maintaining oxygenation, pa ticularly in those patients with limited cardiopulm nary reserve, before induction of anesthesia.

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References

1. Polley PS, Cheney FW. Sodium nitroprusside increases Q_S/Q in dogs with regional atelectasis. Anesthesiology 197 47:338–41.
2. Hill AB, Sykes MK, Reyes A. A hypoxic pulmonary vasoco strictor response in dogs during and after infusion of sodiu nitroprusside. Anesthesiology 1979;50:484–8.
3. Tokioka H, Kobayashi Y, Ohta T, et al. The acute effects prostaglandin E_1 on the pulmonary circulation and oxyge delivery in patients with the adult respiratory distress sy drome. Intensive Care Med 1985;11:61–4.
4. Rademacher PA, Santak B, Becker H, et al. Prostaglandin and nitroglycerine reduce pulmonary capillary pressure b worsen ventilation–perfusion distributions in patients wit adult respiratory distress syndrome. Anesthesiology 198 70:601–6.
5. Kirtland SJ. Prostaglandin E_1. A review. Prostaglandins, Le kotrienes and Essential Fatty Acids—Reviews, 1988;32:165–7
6. Long WA, Rubin LJ. Prostacyclin and PGE_1 treatment pulmonary hypertension. Am Rev Respir Dis 1987;136:773–
7. Killion DD, Ambrus JL. Treatment of complications of perip eral vascular disease with prostaglandin E_1. Angiology 198 38:508–13.
8. Mohrland JS, Porter JM, Smith EA, et al. A multicente placebo controlled double blind study of prostaglandin E_1 Raynaud's disease. Ann Rheum Dis 1985;44:754–60.
9. D'Ambra MN, LaRaia PJ, Philbin DM, et al. Prostaglandin E A new therapy for refractory right heart failure and pulmona hypertension after mitral valve replacement. J Thorac Cardi vasc Surg 1985;89:567–72.
10. Armitage JM, Hardesty RL, Griffith BP. Prostaglandin E_1: A effective treatment of right heart failure after orthotopic hea transplantation. J Heart Transplant 1987;6:348–51.
11. Wagner WW, Lathan LP, Capen RL. Capillary recruitme during airway hypoxia: role of pulmonary artery pressure. Appl Physiol 1979;47:383–7.
12. Naeije R, Melot C, Mols P, et al. Reduction in pulmona hypertension by prostaglandin E_1 in decompensated chron obstructive pulmonary disease. Am Rev Respir Dis 198 124:1–5.
13. Berk JL, Sampliner JE, Artz JS, et al. Handbook of Critical Ca Boston: Little, Brown and Co., 1976:76–80.
14. Shapiro BA, Harrison RA, Trout CA. Clinical Application Respiratory Care. Chicago: Year Book Medical Publishers, Inc 1975:134.
15. Prielipp RC, Rosenthal MH, Pearl RG. Vasodilator therapy vasoconstrictor-induced pulmonary hypertension in shee Anesthesiology 1988;68:552–8.
16. Sandoval J, Long GR, Skoog C, Wood LDH, Oppenheimer Independent influence of blood flow rate and mixed veno Po_2 on shunt fraction. J Appl Physiol Rev 1983;55:1128–33.

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Oscillometric Blood Pressure Determination from the Adult Thumb Using an Infant Cuff

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Key Words: BLOOD PRESSURE, MEASUREMENT—oscillometric. MEASUREMENT TECHNIQUES, BLOOD PRESSURE—oscillometric.

Automatic digital noninvasive blood pressure (NIBP) monitors have become commonly used during anesthesia within the past 10 years. The majority of these are oscillometric units that require the intermittent inflation of a cuff applied to the proximal arm. During the time the cuff is inflated, intravenous access and pulse oximetry monitoring on the same arm are essentially precluded. This limitation can be significant during surgery where only one arm is available. We observed that a small (neonatal) cuff applied to the adult thumb seemed to function well as a way of measuring oscillometric blood pressure. We now report the quantitative performance of a neonatal blood pressure cuff applied to the thumb when used for the noninvasive monitoring of blood pressure in adults.

Methods

With permission of the Institutional Review Board and after obtaining written informed consent, 21 patients who required a radial intraarterial catheter for anesthetic management in general surgery were selected. In each patient, a Dinamap Model 1846 SX oscillometric blood pressure monitor was connected using a neonatal cuff and hosing (supplied with the Dinamap instrument) applied to the thumb. A Spacelabs Model 511 invasive monitor was used to measure invasively arterial pressure via a 20-gauge adial arterial catheter in the wrist contralateral (1) to he thumb cuff connected to a Gould disposable ransducer. The bladder of the neonatal cuff was applied to the volar surface of the thumb. Proper sizing of the cuff was guided by "range" markings on the inside of the cuff that indicate correct fit. Most patients required the "#2" cuff (2.8 cm wide × 4.3–8.0 cm).

Noninvasive oscillometric blood pressure determinations were first performed bilaterally to exclude patients with blood pressure differences between arms due to anatomic factors. An adjustable damping device was inserted into the arterial monitoring system if indicated (2). All systems had a resonant frequency $\geq$25 Hz.

Data were collected from the serial communications ports on each monitor into a computer running automatic data acquisition software recording every 20 sec. Oscillometric readings were initiated by the computer every 2 min for 1 hr. The data were manually screened for obvious artifacts, mainly due to arterial catheter manipulation and sampling of arterial blood, although the noninvasive pressure occasionally (1 reading/hr) read zero. These data were excluded from statistical analysis, because the problem was uncommon and apparently random, and it would be obvious to the observer that these were artifacts.

Precision (mean absolute value of error) and bias (mean error) were calculated for systolic, diastolic, and mean oscillometric pressures using digital invasive pressure as the reference value (3). Briefly, for systolic pressure, for each data point "i,"

$$\mathrm{ERROR}_i = \mathrm{SYSTOLIC}_{\mathrm{oscillometric}} - \mathrm{SYSTOLIC}_{\mathrm{arterial}}.$$

And then for grouped data (Table 1),

$$\mathrm{BIAS}_{\mathrm{systolic}} = \sum_{i=1}^{n} \mathrm{ERROR}_i/n,$$

$$\mathrm{PRECISION}_{\mathrm{systolic}} = \sum_{i=1}^{n} |\mathrm{ERROR}_i|/n.$$

The same calculations were made for diastolic and mean pressures. Data points were taken whenever a

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Table 1. Pooled Precision and Bias for Thumb Oscillometric Blood Pressure Variation with Invasive Pressure Range

Range (mm Hg)	Precision	Bias	Percent error
Systolic			
All	10.8	−3.9	8.4
60–89	6.7	−0.8	8.3
90–119	8.6	1.5	7.9
120–149	10.4*	−4.0	7.9
150–179	16.3*	−16.3	10.1
180+	28.1*	−28.1	14.6
Diastolic			
All	8.3	0.2	12.7
40–49	8.6	2.0	18.5
50–69	7.9	−1.0	12.9
70–89	9.0	1.3	11.8
90+	10.7	6.4	10.6
Mean			
All	10.8	−3.9	10.2
50–69	7.1	−1.1	11.4
70–89	8.4	1.7	10.3
90–109	9.8*	0.5	10.0
110–130	11.2*	−6.7	9.7
130+	12.2	0.2	8.8

*A significant ($P < 0.05$) difference from the lowest pressure range.

new oscillometric reading became available (every 2 min). Changes in precision and bias as a function of pressure were evaluated by dividing data points into five (systolic and mean) or four (diastolic) pressure groups based upon arterial pressure and *t*-testing each group against the group with the best (smallest) precision. Differences were considered significant if the mean values differed by more than 5 mm Hg and the *P*-value was less than 0.05. "Percent error" was calculated for each data point by dividing the precision by the arterial pressure. Patients were queried upon initiation of oscillometric pressures and postoperatively in the recovery room regarding any discomfort or paresthesia.

Results

Twenty-one patients were studied, and data from 20 were analyzed. The one patient excluded had no measurable thumb pressure due to a thrombosed radial artery. Patient ages ranged from 21 to 84 years (mean = 57). The first 25 data sets (50 min) from each patient were selected for analysis, since this represented anesthetic induction, where blood pressure transients were likely. There were no complications or discomfort associated with the use of the thumb cuff.

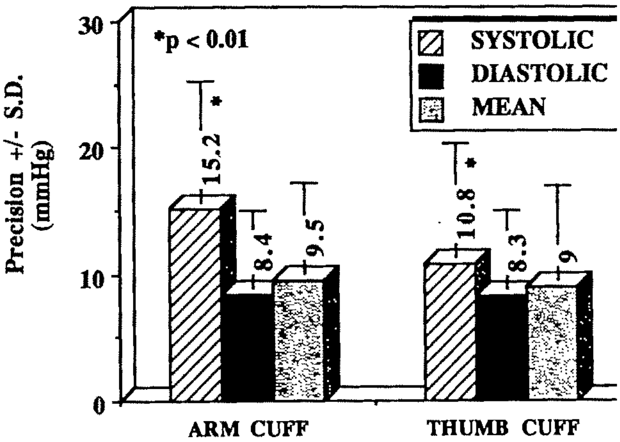

Figure 1. Pooled precision (mean absolute error) for all patients all pressure ranges. "ARM" (Brachial) data from previous stu (4).

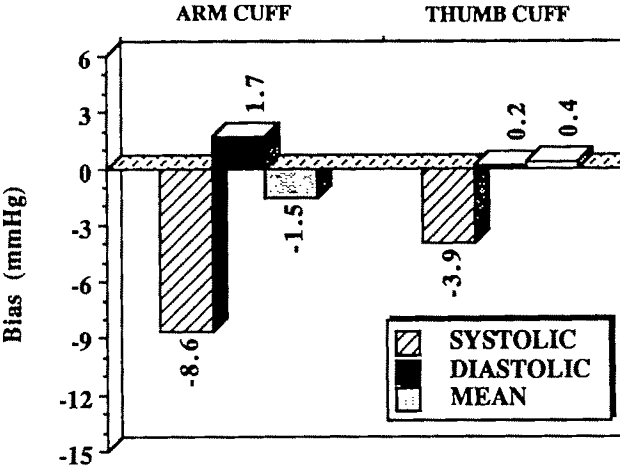

Figure 2. Pooled bias (mean error) for all patients in all pressu ranges. "ARM" (Brachial) data from previous study (4).

Pooled precision and bias data are shown in Fi ures 1 and 2. In many patients, the magnitude of t bias was similar to that of the precision, suggesti that a consistent error was occurring. In other p tients, however, the magnitude of the bias was mu smaller than the precision, indicating that the inacc racy was bipolar and perhaps random.

Systolic precision was best at lower pressures, a deteriorated as arterial pressure increased (Figure and Table 1). The worst (largest) systolic precisi values (16 and 28 mm Hg) were obtained for the tv groups with invasively measured systolic pressu ≥150 mm Hg. The magnitude of the bias in the tv worst groups was the same as the precision, sugge ing consistent underestimation of arterial pressure the source of the error. The best (smallest) systo precision (7, 9, and 10 mm Hg) occurred in the thr groups with invasively measured systolic pressu <150 mm Hg. Displaying the precision in terms

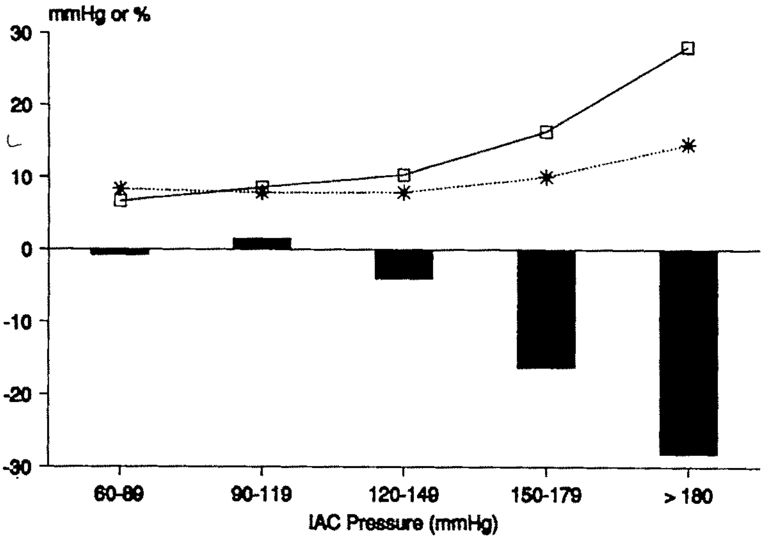

Figure 3. Variation of systolic precision and bias for thumb oscillometric pressure as a function of invasive arterial pressure (IAC). *"Percent error" (see text), □ = precision, ■ = bias.

"percent error" (Figure 3 and Table 1) still demonstrated a larger error in the two groups with invasively measured systolic pressure >150 mm Hg.

The diastolic precision did not differ significantly among the four diastolic pressure groups and was approximately 10 mm Hg with negligible bias (Table 1). Diastolic "percent error" was approximately 13%. Not surprisingly, precision and bias for the mean pressure fell between the corresponding systolic and diastolic values. We did not find any clinically significant differences among mean pressure groups.

Discussion

The pooled results of this study as well as those of our previous study (4) measuring similar data for brachial noninvasive blood pressure with the same monitor are both presented in Figures 1 and 2 for comparison. In general, placement of a neonatal cuff on the thumb connected to an unmodified Dinamap Model 1846 SX oscillometric monitor produces blood pressure values that reflect invasive arterial pressure as well as or better than conventional arm placement. Both methods are reasonably accurate at "normal" pressures, but performance deteriorates in hypertensive individuals (Figure 3 and Table 1), with predictable underestimation of systolic arterial pressure. This observation is consistent with the findings of Loubser (5) for brachial oscillometric pressure. The accuracy of the thumb cuff oscillometric method was not evaluated in this study during severe hypotension.

Interference with ipsilateral pulse oximetry and intravenous access is eliminated by use of a thumb cuff, and there is no significant patient discomfort. In addition, the Dinamap Model 1846 SX obtains readings considerably more rapidly from the thumb than it does from the arm, since the air volume of the cuff and tubing is much smaller than that of a standard brachial cuff.

References

1. Kurki TS, Sanford TJ, Smith NT, Dec-Silver IT, Head N. Effects of radial artery cannulation on the function of finger blood pressure and pulse oximeters. Anesthesiology 1988;16:778–82.
2. Gardner RM. Direct blood pressure measurement—Dynamic response requirements. Anesthesiology 1981;54:227–36.
3. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. J Pharmacokin Biopharm 1981;9:503–12.
4. Gorback MS, Quill TJ, Graubert DS. An evaluation of two rapid non-invasive blood pressure methods during general anesthesia induction. Anesth Analg 1989;68:S106.
5. Loubser PG. Comparison of intra-arterial and automated oscillometric blood pressure measurement methods in postoperative hypertensive patients. Med Instrum 1986;20(5):255–9.

ANESTH ANALG 67
1989;69:671–3

Interpleural Analgesia in Treatment of Upper Extremity Reflex Sympathetic Dystrophy

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Key Words: SYMPATHETIC NERVOUS SYSTEM, REFLEX DYSTROPHY. ANESTHETIC TECHNIQUES, REGIONAL—interpleural.

Many diverse recommendations for the treatment of reflex sympathetic dystrophy (RSD) have been offered in the past few years. It is now apparent that early aggressive treatment is an important key to successful treatment. Although the mechanism causing RSD remains unknown, sympathetic blockade with local anesthetics is the foundation of management. In the past year we have treated seven patients with severe upper limb RSD by giving daily injections of 30 mL of 0.5% bupivacaine with epinephrine (5 μg/mL) through an interpleural catheter percutaneously inserted through the fourth intercostal space.

Methods

Seven patients with the diagnosis of RSD of the upper extremity entered into the treatment program as outpatients. Each patient met at least five of the most important clinical RSD criteria: allodynia or hyperpathia, edema, burning pain, sweating changes, color or hair growth changes, skin atrophy, temperature changes, and radiographically verified demineralization. A history of previous surgical or accidental trauma to the affected extremity was elicited from all patients. Neurological examinations showed no evidence of peripheral nerve damage in any patient.

Because of the disappointing results of previous treatment regimens, interpleural catheters were inserted percutaneously after obtaining written informed consent from all patients. Each patient rate their pain using a verbal analogue pain scale from 0 t 10 with 0 as pain-free and 10 reflecting the wor imaginable pain. Pain scores were elicited before eac injection of local anesthetic, every minute for the fir 10 min after injection, and on return of pain when th effect of the local anesthetic wore off. Using th previously described method, a 16 SWG epidur catheter was inserted through the fourth intercost space a distance of 6–10 cm (1). A sterile plast dressing and micropore filter were attached. With th patient in the lateral decubitus position with th affected side up and the head down 20°, 30 mL 0.5% bupivacaine with epinephrine (5 μg/mL) wa injected over 6 min after negative aspirations f blood and air. Thirty minutes after each interpleur injection of local anesthetic the patients were teste for sympathetic blockade of the upper limb by mea suring changes in skin temperature in the hand an observation for ipsilateral Horner's syndrome. To te the effect on the brachial plexus we tested sensor function in cutaneous dermatomes using a pin pric and cold swab to determine the extent and degree analgesia. A physiotherapist tested muscle strengt and joint range of motion for the major muscles of th shoulder and upper extremity. To test for abolition sweating we used the cobalt blue filter paper test. Th test paper was placed on a clean surface and th patients pressed their palms to the paper resulting i a pink pattern on the nonaffected side and no colo change on the affected side. Blood pressure, hea rate, and respiration were monitored by a traine nurse for 1 hr after each injection.

A chest x-ray was taken 2 hr after insertion of th interpleural catheter to rule out pneumothorax. Th patients were informed about the symptoms of pneumothorax and told to come to the emergenc room immediately if any symptoms developed. A pain medications were discontinued during trea ment. We used what we call a steady state techniqu

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Table 1. Patient Characteristics

Patient No.	Sex (M/F)	Age (years)	Injury	Duration of pain (months)	Initial pain score*
1	M	38	Humerus fracture R	7	9
2	M	53	Humerus fracture L	4	10
3	F	71	Humerus fracture R	23	10
4	M	45	Humerus fracture R	3	10
5	M	35	Cervical rib resection R	2	10
6	F	48	Soft tissue injury R arm	3	10
7	M	61	Soft tissue injury R arm	2	9
Mean		50.1		6.3	9.7
SD		12.7		7.6	0.5

*Pain score based on initial verbal analogue report before treatment. SD: standard deviation.

Table 2. Pain Scores During and After Treatment

Patient No.	PS p 1st	Onset (min)	Duration (hr)	PS return	# Inj	PS final	FU (months)
1	0	7	10	5	15	2	9
2	0	6	22	2	19	0	10
3	5	6	8	7	14	4	8
4	3	5	12	5	10	1	4
5	2	7	12	5	14	1	5
6	1	7	16	4	14	0	6
7	0	6	18	3	14	0	5
Mean	1.5	6.3	14	4.4	14.2	1.1	6.7
SD	1.9	0.8	4.9	1.6	2.6	1.4	2.3

PS p 1st: verbal analogue pain score after first injection, maximum relief achieved; onset: time to maximum relief in minutes after interpleural injection; duration in hours of pain relief after first injection; PS return: verbal analogue pain score on return of pain after first injection; PS final: final verbal analogue pain score after completion of treatment cycle; FU: duration of follow-up in months; SD: standard deviation.

A patient is said to be in a steady state when his or her pain is no longer decreasing in spite of repeated interpleural injections. All patients received a daily injection on each of 5 days after they were pain-free or had reached a steady state.

Results

Patient characteristics are described in Table 1. Before visiting our pain clinic patients 1, 3, and 6 had achieved only temporary relief from repeated stellate ganglion blocks. Patient 7 had several previous intravenous guanethidine blocks with poor results. All patients were using high doses of potent analgesics, including narcotics in some instances. Sleep patterns were disrupted in all patients, and six were unemployed.

All the patients developed a profound sympathetic block of the ipsilateral upper extremity immediately after the first injection. The temperature of the affected limb increased 3° to 9°C in all patients, with the largest temperature increase in the patients with the lowest starting temperature. The increase in skin temperature and the relief of pain were associated with abolition of sweating and an ipsilateral Horner's syndrome after every injection. The Horner's syndrome developed 15 to 45 min after the injection and lasted 6 to 8 hr. Five to seven minutes after the start of the injection three patients were completely pain-free, three had minimal pain, and the patient with the longest duration felt that her pain was only half as bad as before the injection. Pain relief lasted for 10 to 22 hr. When the pain did return as the block wore off, it was at a significantly lower level than before the treatment with interpleural injection in all patients.

The interpleural injections also blocked portions of the ipsilateral brachial plexus. Hypesthesia in all dermatomes from C3 to T1 with a reduced muscular strength developed after each injection. This persisted for up to 14 hr. All patients initially had severe limitation of shoulder and elbow movements, but after each block rigorous physiotherapy of these joints could be easily performed without pain. After completion of the treatment cycle, all patients with one exception had normal range of motion of the shoulder and elbow. The female patient with the longest duration of RSD before treatment did not regain full active and passive range of motion although she did experience a marked improvement. There were no complications related either to the catheter, its insertion, or injections of anesthetic solutions during the treatment.

The results were encouraging. During the follow-up periods, which ranged from 4 to 10 months, three of the patients were completely pain-free; three had only minimal pain requiring no medication; the last patient with the most severe upper limb RSD had a steady state pain that could be treated with minor analgesics and that allowed her to return to a normal life (Table 2). The patients were seen at our Pain Clinic once a week for the first month, then every 2 to 3 weeks for the duration of the follow-up period. They were told to inform us of any return or increase in the pain. All patients have maintained the same degree of analgesia, which they reached while undergoing treatment, during the follow-up period of 10 months. Six of the patients who were not working when they presented for treatment have now returned to work.

Discussion

Several methods have been used for management of upper extremity RSD. Wang et al. reported good results using repeated stellate ganglion blocks: 74% of their 31 patients improved at the time of their 3-year evaluation (2). However, patients with an RSD history of more than 1 year were excluded from their study. Sixteen of 31 patients had only partial or no improvement. Two patients had in fact deteriorated. Also, their study included 15 patients with peripheral nerve injuries. The best results in their study were found in patients without nerve injury and with a short interval between onset of symptoms and the start of treatment. Interscalene blocks have also been used in the management of RSD with some success (3). Intravenous guanethidine, an adrenergic ganglionic blocker, has also been tried (4). Despite our relatively small group of patients and short observation time, we believe that our results indicate that interpleural analgesia may be very useful in the treatment of upper limb RSD. By positioning the patients as described with the afflicted side uppermost, the local anesthetic solution injected in the pleural space should easily diffuse through the medial surface of the parietal pleura and block the cervical portion of the sympathetic chain, including the stellate ganglion. However, the stellate ganglion is quite variable in size and position and may not represent the fusion of the inferior cervical and first thoracic ganglia. If it in fact does not, this anatomic variation may make it difficult to obtain good results when attempting direct blockade of the stellate ganglion. Interpleural catheter analgesia with correct positioning of the patients may give a more predictable block of the stellate ganglion and can be repeated with reinjection of an indwelling catheter rather than reinsertion of a needle near the other structures of the neck, including the vertebral artery, the subarachnoid space, and the epidural space. Another important detail is that interpleural analgesia as described here seems to provide a reasonable blockade of the brachial plexus and makes physical therapy during the course of RSD treatment possible and more tolerable for the patient.

Our results confirm those of Wang et al. in demonstrating how important it is to start an aggressive treatment program in RSD patients as soon as the diagnosis has been confirmed. Delay in referral of the patient to the pain clinic makes the treatment more difficult and reduces the chances of complete success We believe that continuing the interpleural injectio for 5 days after complete pain relief or a steady stat is achieved may contribute to a prolonged duration o relief of pain and disability. Only further trials wil show if this theory is correct.

Seven patients with severe upper extremity RS were treated with injections of 30 mL of 0.5% bupivacaine with epinephrine (5 μg/mL) using an interpleural catheter placed through the fourth intercosta space on the affected side. By positioning the patient in the lateral decubitus position with the affected sid up and head down about 20° for 30 min after th injection a profound sympathetic block was produce in all patients. A partial block of the ipsilateral brachial plexus was also achieved. This resulted in a immediate onset of a significant degree of analgesia lasting up to 22 hr, in all patients. Physical therap was performed without difficulty or pain during thi period. The same anesthetic solution was injecte daily through the catheter for 10 to 19 days depending on response. Six of the patients showed complet pain relief for 2 to 8 months. All patients regaine good joint movements and muscular function in th affected extremity. No side effects related to the dru or the catheter were noted during the treatmen period. Further evaluation will be necessary to determine the value of this technique in treating RSD.

Our results are only preliminary, but they see promising. Interpleural analgesia is easy to perform it is safe and causes few complications when don correctly. The catheter itself produces only minima discomfort for the patient during the insertion.

References

1. Reiestad F, Strømskag KE. Interpleural catheter in the management of postoperative pain: a preliminary report. Reg Anest 1986;11:89–91.
2. Wang JK, Erickson RP, Ilstrup DM. Repeated stellate ganglio blocks for upper extremity reflex sympathetic dystrophy. Re Anesth 1985;10:125–8.
3. Gibbons JJ, Wilson PR, Lamer TD, Gibson BE. Interscalen blocks for chronic upper extremity pain. Reg Anesth 1988;13:5
4. Bonelli S, Conoscente F, Movilia PG, et al. Regional intravenou guanethidine versus stellate ganglion blocks in reflex sympathetic dystrophies: a randomized trial. Pain 1983;16:297–307.

674 ANESTH ANALG
1989;69:674–6

Contaminated Oxygen Cylinder

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Key Words: OXYGEN, CYLINDERS—contamination. EQUIPMENT, OXYGEN CYLINDERS—contamination.

Potential sources of lay public exposure to stored oxygen supplies include commercial aircraft decompression, mountain climbing at high altitudes, and emergency medical rescue activities. Hospitalized patients are exposed to supplemental oxygen, the most commonly used medical gas, from two sources: pipeline supplied oxygen from a central tank storage system or gas delivered from small portable cylinders. Despite reports of central oxygen supply contamination or misconnections, clinicians usually assume that the gas source is pure (1–4). Perhaps justifiably, even greater reliance is placed on the purity of the contents of small oxygen cylinders.

The standard of care in anesthesia requires monitoring of the inspired oxygen concentration during general anesthesia. In some operating rooms, complex systems, such as the mass spectrophotometer, repetitively analyze the composition of both the inspired and exhaled anesthetic gas mixture. Outside of the operating room, gas monitoring is uncommon, except for an occasional spot check in intensive care units. Monitoring of cylinder supplied gases during transport ventilation of patients is almost nonexistent.

This report details the use of what was subsequently recognized to be a contaminated oxygen cylinder during transport ventilation of a hospitalized patient. A 54-year-old, 120-kg, 163-cm woman presented for elective tracheostomy 23 days after hospi-alization for an emergency right parietal craniotomy o manage an intracerebral hemorrhage. At the time of admission, she had a blood pressure of 230/110 mm Hg. Past medical history was significant for hyper-ension complicated by a cerebral vascular accident, morbid obesity, and renal failure.

The patient, who was comatose and intubated throughout her hospitalization, remained ventilator dependent and was scheduled for tracheostomy. During preoperative transportation to the operating room from the neurosurgical intensive care unit, monitoring included blood pressure by arterial catheter, electrocardiogram, and heart rate, as well as oxygen saturation by pulse oximetry. Ventilation was controlled manually with a Pulmanex bag-valve system with oxygen supplied through a regulator and flowmeter from an E size cylinder lying flat on the patient's bed. Monitored vital signs were stable throughout.

During the tracheostomy, general anesthesia was maintained with fentanyl and vecuronium IV and oxygen by endotracheal tube with controlled ventilation provided by a ventilator equipped anesthetic machine using the central oxygen supply. The tracheostomy site was also infiltrated with use of lidocaine 1% with epinephrine 1:100,000.

Surgical and anesthetic management was uneventful. After placement of the tracheostomy and reestablishment of ventilation with use of the anesthesia machine, transport monitors were reconnected. The oxygen cylinder and bag-valve system, previously used to ventilate the patient during transport from the neurosurgical intensive care unit, was again used to provide 8 L of gas flow/min. The tank lay horizontally on the air inflated mattress on the bed. After positioning the patient in her bed, electrical power was intentionally disconnected and the mattress allowed to deflate. This resulted in the top of the oxygen cylinder becoming dependent. Immediately, a rusty colored liquid filled the flowmeter and connecting tubing and flowed into the bag-valve apparatus. Ventilation continued with use of the anesthesia machine while a new E cylinder and bag-valve system were obtained. The patient was returned to the neurosurgical intensive care unit without further incident.

Postoperative assessment revealed no adverse effects. The patient was eventually weaned from the ventilator and was transferred to a general care area

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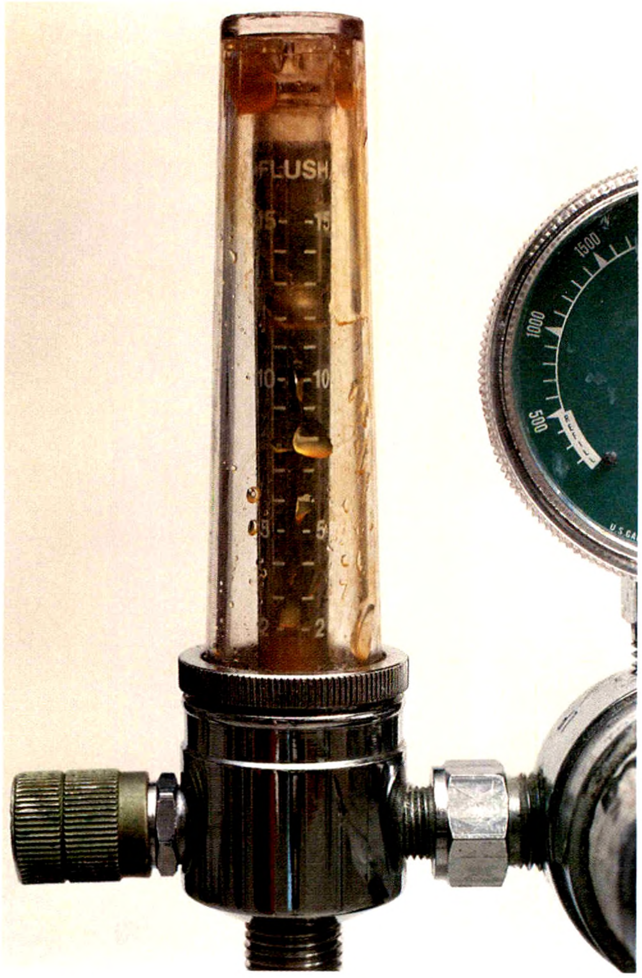

Figure 1. Contaminated cylinder and flowmeter.

with the tracheostomy still patent. Two months later, her condition remained unchanged. Her only response was withdrawal from painful stimuli. Her hypertension was controlled by medication, and arterial blood gas tensions remained satisfactory during spontaneous ventilation.

Analysis of Tank Contents

The tank, regulator, and bag-valve system were immediately taken to our Medical Illustration Department where appropriate photographs were made (Figure 1). Gas from the cylinder was then analyzed by gas chromatography/mass spectrometry (GC/MS) with use of purge and trap introduction. No volatile organic compounds were found. When the tank was inverted, a reddish-colored liquid was collected, one sample of which was allowed to stand for 2 days. The red coloring settled to the bottom and appeared to be rust. Analysis by inductively coupled plasma emission spectrophotometer showed iron levels of 250 ppm, confirming that the coloration was rust. The liquid itself was found to be water by gas chromatography.

The water was extracted with methylene chloride and analyzed by GC/MS. Two organic compounds were observed, both at levels below 1 ppm. They were 2-butyl cellosolve and caprolactam, both commonly used in formulations of paint and lacquer.

The interior of the plastic tubing was also extracted with methylene chloride and analyzed by GC/MS. Organics observed were 2-octanone, *n*-decanol, BHT, isoamyl benzoate, and nonylphenol, all at minute levels. The first two are components of paint; the last three are antioxidants and/or stabilizers, presumably from the tubing itself. The cost of these analyses was $1,020.00.

Discussion

It is quite clear that a serious complication was averted only by a combination of events commonly referred to as luck. Had the bag-valve system been connected to the patient at the time of bed deflation and tank inversion, the patient would almost certainly have had this liquid forced into her lungs. If the tank had become inverted during transportation without a second ventilating system being readily available, the patient would have required mouth to tracheostomy ventilation, or to avoid the hypoxia associated with ventilation at an $F_{I_{O_2}}$ of 0.16, would have had the liquid unavoidably forced into her airway.

The source of the rusty water is uncertain. The supplier of the cylinder (Liquid Carbonic—lot No. PAF238H) confirms that the cylinders are filled from a bulk source of liquid oxygen. The cylinders, internally inspected before filling, are not inverted before filling and remain upright during the filling process, which uses a manifold system. Every 5 years, the tank valve is removed and the interior inspected with a fiberoptic viewing device. The other cylinders in this lot showed no signs of contamination. Furthermore, the method of manufacturing and liquefying the oxygen removes almost all moisture. The filling process does not appear to be the source of the water.

The supplier suggested that a cylinder connected to a humidifier could be contaminated by water draining back into the cylinder from the humidifier, after the oxygen supply in the cylinder was exhausted. We are unable to confirm this possibility at this time in our hospital. However, because the supplier provides cylinders, using a central pool, to several other hospitals in the city, a different style of humidifier used elsewhere might have been the source of the contamination.

If this mechanism of contamination were common, however, an event such as the one we now report would be expected to be known to members of the anesthesiology, respiratory care, or central supply departments, to have been shown as a warning on the cylinder, or to have been described elsewhere. This occurrence has not been reported elsewhere and was unknown to the personnel in our hospital, which purchased 4664 E-cylinders of oxygen in the 12 months preceding this episode and in excess of 40,000 in the preceding 10 years.

Our recommendations for avoiding the circumstances explained in this case report are to 1) request the supplier of oxygen cylinders to verify the absence of liquid phase contaminants before refilling; 2) avoid the top dependent position for in use oxygen cylinders; or 3) before patient ventilation, cylinders used for transport usage should be inverted with the cylinder valve open and the flowmeter set to the expected flow rate.

References

1. Smith FFP. Multiple deaths from argon contamination of hospital oxygen supply. J Forensic Sci 1987;32:1098–102.
2. Bancroft ML, duMoulin GC, Hedley-Whyte J. Hazards of hospital bulk oxygen delivery systems. Anesthesiology 1980; 52:504–10.
3. Feeley TW, McClelland KJ, Malhotra IV. The hazards of bulk oxygen delivery systems. Lancet 1975;28:1416.
4. Clydesdale P. How safe is your hospital's oxygen storage tank? Hosp Top 1978;56:22–3.

T-Wave Changes Associated with Electroconvulsive Therapy

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Key Words: ANESTHESIA, ELECTROCONVULSIVE THERAPY. IONS, SERUM POTASSIUM. NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE—potassium levels.

Electroconvulsive therapy (ECT) is used to treat severe psychiatric depression. Various cardiac arrhythmias have been described during ECT (1,2). This report describes the occurrence of large upright T waves (Figures 1 and 2) during ECT, which, to our knowledge, has not previously been described.

Report of a Case

A 68-year-old white male with severe depression refractory to oral antidepressants without other significant medical problems was scheduled for ECT. He was receiving no medications and his preoperative electrocardiogram (ECG) and laboratory data including blood electrolyte levels were within normal limits. ECG (lead II) and blood pressure were monitored for each of his 10 ECT treatments. The patient was preoxygenated, circulation in right arm occluded with a blood pressure cuff, anesthesia induced with 80 mg methohexital, and muscle relaxation obtained with 100 mg succinylcholine. The patient was manually hyperventilated for 1 min prior to ECT. Concurrent with the ECT-induced right arm seizure, ECG (lead II) showed increased T-wave amplitude (from 6 mm to 15 mm). No other ECG changes were noticed. Hyperkalemia was suspected and venous blood for measurement of plasma potassium (K^+) was obtained (later reported as 4.2 mEq/L). Heart rate and arterial blood pressure returned to normal within 3 min after the seizure, and the T wave returned to normal after another 7 min. During the next treatment of the same patient, blood samples were obtained for measurement of plasma K^+ levels to evaluate the possible role of K^+ as the cause of the ECG changes observed. The results are shown in Table 1. The patient received a total of 10 ECT treatments, and similar increased T-wave amplitude occurred during each ECT session.

Since that observation, we studied 51 additional patients undergoing ECT and looked for T-wave changes similar to those described in this report. Observations were made of 31 female and 20 male patients diagnosed with severe depression. None was receiving medication and the preoperative ECG and serum electrolyte levels were within normal limits. The average age of the group was 59 ± 11 years, and each was studied during the initial ECT of their series. Concurrent with ECT-induced right arm seizure, 11 patients demonstrated an increased T-wave amplitude (2 ± 0.3 mm to 5 ± 0.5 mm) on lead II (Figures 3 and 4) lasting for an average of 6 ± 1 min. No other ECG changes were noted. K^+ levels were not measured in these cases.

Discussion

The patient described here illustrates that T-wave changes suggestive of hyperkalemia appeared following ECT.

Increase in the amplitude of T waves occurs with K^+ values of 7 mEq/L (1) and over and is described as narrow and tented with widened QRS. Marked hyperkalemia is likely to occur during anesthesia when succinylcholine is administered to patients with extensive burns, muscle trauma, denervation paraple-

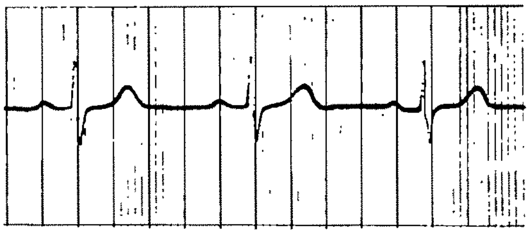

Figure 1. Patient A before ECT. Paper speed, 50 mm/sec.

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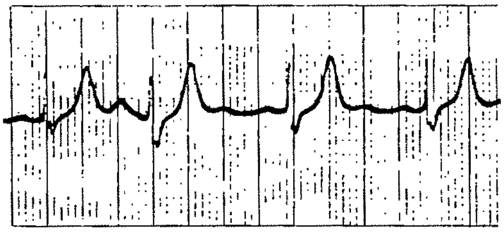

Figure 2. Patient A after ECT. Paper speed, 50 mm/sec.

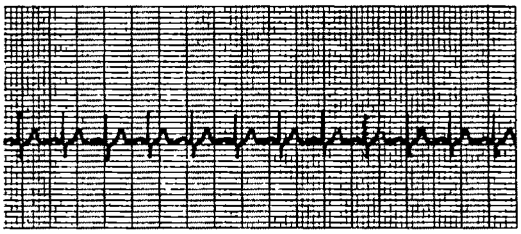

Figure 3. Patient B before ECT. Paper speed, 12.5 mm/sec.

Table 1. Potassium Levels during ECT Treatment in the Patient Described in the Case Report

	Before ECT	30 sec p sux	60 sec p sux	1 min p ECT	2 min p ECT	5 min p ECT	10 min p ECT	15 min p ECT
Potassium (mEq/L)	4.3	4.4	4.7	4.6	4.2	4.6	4.5	4.6

p = post; sux = succinylcholine.

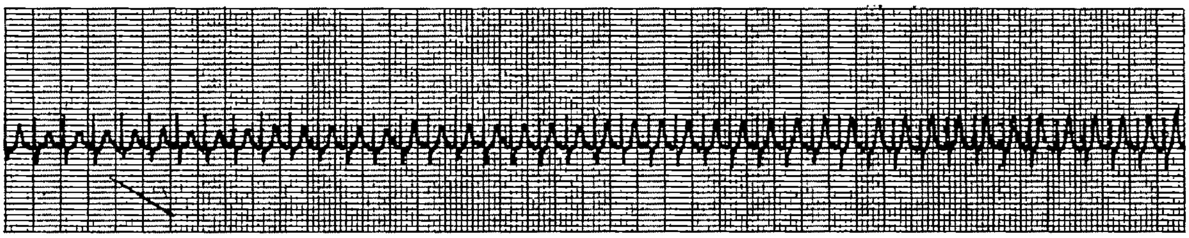

Figure 4. Patient B after ECT. Paper speed, 12.5 mm/sec.

gia, and prolonged immobilization. Our patient did not suffer from any of these conditions.

ECT alone is unlikely to cause severe hyperkalemia as demonstrated by Valentin et al. (3) who found that plasma K^+ levels increase only by 0.25 mEq/L in patients given succinylcholine followed by ECT, whereas for patients given succinylcholine without ECT the increase averaged 0.1 mEq/L. Our patient had similar K^+ level changes (Table 1).

Changes in the ST segment and T wave can be produced in experimental animals either by stimulation or destruction of the central nervous system (4–6). Stimulation of the ventral hippocampus and amygdala in cats produces ST–T-wave abnormalities. Yanowitz et al. (5) demonstrated in dogs that direct stimulation of the cervical sympathetic nerves shortens the ventricular refractory period and that ablation of these nerves lengthens the refractory period. Furthermore, these interventions were associated with ST–T-wave changes. These workers also demonstrated that the right cervical sympathetic nerves principally influence the refractory periods in the anterior ventricular wall, whereas the left sympathetic nerves mainly affect the posterior ventricular wall. In particular, right stellate ganglionectomy or left stellate stimulation produce prolonged ST intervals and increased T-wave amplitude. Left stellate ganglionectomy or right stellate stimulation, on the other hand, produce T-wave negativity without measurable change in the QT interval. Thus, changes in sympathetic tone in experimental animals can produce ECG effects that resemble those seen in patients with lesions of the central nervous system.

Burch (7) et al. have also stressed that the ECG changes in cerebral vascular accidents suggest sympathetic storms resulting from cerebral injury.

During ECT, discharge of the autonomic nervous system is marked. This adrenergic stimulation may influence the development of both supraventricular and ventricular arrhythmias (8). Similarly, the marked adrenergic stimulation may also produce T-wave alterations in the ECG. This is conjectural, but animal research supports this contention.

In summary, patients undergoing ECT may exhibit increased T-wave amplitude, which can simulate hyperkalemia. It is important to measure K^+ levels once to rule out hyperkalemia before starting any unnecessary treatment. If the K^+ blood level is normal, it can be assumed in subsequent ECT treatments that the increased T-wave amplitude is due to sympathetic imbalance, and it is unlikely that these ECG alterations are of any clinical importance.

References

1. Altschule MD. Further observations on vagal influences on the heart during electroshock therapy for mental disease. Am Heart J 1950;39:88–91.
2. Hejtmanck MD, Bankhead AJ, Hermann GR. Electrocardiographic changes following electroshock therapy in curarized patients. Am Heart J 1949;37:790–805.
3. Valentin N, Skovsted P, Danielsen B. Plasma potassium following suxamethonium and electroconvulsive therapy. Acta Anaesthesiol Scand 1973;17:197–202.
4. Porter RW, Kamikowa U, Greenhoot JH. Persistent electrocardiographic abnormalities experimentally induced by stimulation of the brain. Am Heart J 1962;69:815–9.
5. Yanowitz F, Preston JB, Abildskov JA. Functional distribution of right and left stellate innervation to the ventricles: production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone. Circ Res 1966;18:416–28.
6. Rogers MC, Abildskov JA, Preston JB. Cardiac effects of stimulation and block of the stellate ganglion. Anesthesiology 1973; 39:525–33.
7. Burch GE, Meyers R, Abildskov JA. A new electrocardiographic pattern observed in cerebrovascular accidents. Circulation 1954; 9:719–23.
8. Gould L, Basili R, Reddy CVR. Utility of monitored electroconvulsive therapy apparatus. NY State J Med 1981;81:406–8.

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Comparison of the Effects of Oral Famotidine and Ranitidine on Gastric Volume and pH

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Key Words: GASTROINTESTINAL TRACT, STOMACH—famotidine, ranitidine. HISTAMINE, FAMOTIDINE, RANITIDINE.

Aspiration of acidic gastric contents during the perioperative period has been a continuing concern to anesthesiologists since the days of Hannah Greener (1). The acidity (pH < 2.5) (2) and volume (>25 mL or 0.3 mL/kg of normal body weight) (3) of gastric contents have been suggested as factors associated with significant morbidity when aspiration does occur. With the recognition of the H_2 receptor and its association with gastric acid production by Ash and Scheld (4) in 1966, emphasis has been placed on producing newer and safer H_2-receptor antagonists. Compounds have included burimamide, metiamide, cimetidine, and ranitidine. Both cimetidine and ranitidine, despite some untoward side effects (5), have withstood the test of time and are still currently prescribed for clinical use. The most recent drug to be introduced is famotidine, which differs structurally from previous drugs by the presence of a guanylthiazole ring. It is 3–20 times more potent than ranitidine with a 30% longer duration of action (6).

The efficacy of cimetidine and ranitidine in decreasing gastric volume and increasing gastric pH and so perhaps providing prophylaxis against aspiration pneumonitis in surgical patients has been shown (7–9). The efficacy of famotidine remains to be evaluated. The purpose of this study was to compare the effectiveness of famotidine, ranitidine, and placebo in reducing gastric volume and gastric acidity in outpatients, a group with an increased risk for acid aspiration (10).

Methods

Eighty-three ASA physical status 1 and 2 adult outpatients scheduled for elective surgery under general anesthesia were recruited. Patients with gastrointestinal disorders were excluded. The study was approved by the institutional Internal Review Board for Human Research and informed consent was obtained from all patients. The patients were divided into five groups and for blinding purposes into two sections. Section one consisted of groups 1, 2, and 3. Section two consisted of groups 4 and 5. Within each section, patients were randomly assigned in a double-blinded fashion to one of the groups. Patients in group 1 received an oral placebo, group 2 received one pill of famotidine 40 mg, and group 3 one pill of an equipotent dose (6) of ranitidine, namely, 150 mg. The pill was placed in a brown paper envelope and the patient was instructed to take the pill on retiring on the night before surgery. Group 4 received two pills of famotidine 40 mg each and group 5 received two pills of ranitidine 150 mg each. These patients were instructed to take one pill on retiring the night before surgery and one pill on arising the morning of surgery. Patients received no other premedications.

On arrival in the operating room, the patients were questioned as to the time their medication was taken. The time of anesthesia induction was noted after which anesthesia was induced with thiopental and the trachea intubated with use of a muscle relaxant. A No. 18 Salem sump tube was then passed into the stomach and gastric contents were aspirated into a mucus trap. The patients were tilted side to side and placed in the 45° head-down position to facilitate gastric aspiration.

The volume of the gastric aspirate and the pH (Cole Palmer Model 5985-75 pH Wand) were determined and recorded immediately in the operating room.

Statistical analyses included analysis of variance

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Table 1. Summary Results

Group	No. of patients	Height (cm)	Weight (kg)	Interval from last pill (min)	pH	Volume (mL)
1 Placebo	15	162 (±9.9)	70 (±18)	720 (±135)	2.16 (±1.7)	19.9 (±15.4)
2 Famotidine PM	15	167 (±8.1)	72 (±15.9)	741 (±133)	3.8 (±2.2)	17.7 (±14.9)
3 Ranitidine PM	15	164 (±6.4)	68 (±21.7)	668 (±104)	4.3* (±2.1)	17.9 (±11.7)
4 Famotidine PM and AM	8	166 (±9.1)	60 (±13.2)	163 (±65)	6.2* (±1.9)	7.8* (±7.2)
5 Ranitidine PM and AM	12	165 (±9.6)	74 (±18.5)	179 (±58)	6.5* (±1.8)	11.3* (±5.8)

Height, weight, interval (time from pill ingestion until sampling), pH, and volume in each group (*significantly different from placebo [$P < 0.05$]). Results expressed as mean ± SD.

(ANOVA) and Student's *t*-test. Results were considered significant if *P* values were <0.05.

Results

Sixty-five patients were included in the study. Eighteen patients were disqualified due to noncompliance with protocol or case cancellation, resulting in uneven group distribution. There was no significant difference between groups in relation to gender, height, or weight. Between groups 1, 2, and 3 and groups 4 and 5, there were no significant differences in the interval from pill ingestion to gastric sampling. All patients fasted for at least 8 hr before sampling. In two patients, we were unable to obtain gastric volumes adequate for measurement of pH. Results are shown in Table 1.

Table 2. Distribution of High Risk Groups

Group	No. of patients	No. of patients with pH <2.5	No. of patients with vol >25 mL	No. of patients with pH <2.5 and vol >25 mL
1 Placebo	15	13/15	6/15	5/15
2 Famotidine PM	15	7/14*	5/15	3/15
3 Ranitidine PM	15	4/15	5/15	2/15
4 Famotidine PM and AM	8	1/7*	0/8	0/8
5 Ranitidine PM and AM	12	1/12	0/12	0/12

Values are actual number of patients in each group. *Inadequate volume to measure pH in one patient in group.

Gastric pH

There were significant differences in gastric pH between placebo and groups 3, 4, and 5. Both famotidine and ranitidine, when an additional dose was given in the AM, significantly increased pH to >2.5. Ranitidine, but not famotidine, when taken only the night before surgery, without a morning dose, significantly increased pH when compared with placebo. However, when comparing group 2 (famotidine) with group 3 (ranitidine), there was no significant difference between groups. When comparing group 3 (PM ranitidine) with group 5 (PM and AM doses of ranitidine), the double dose regimen was significantly more effective. The numbers of patients with pH <2.5 are shown in Table 2. Figure 1 depicts the percentage of patients in each group with gastric pH <2.5.

Gastric Volume

The two groups (groups 4 and 5) receiving AM and PM doses had significantly reduced gastric volumes

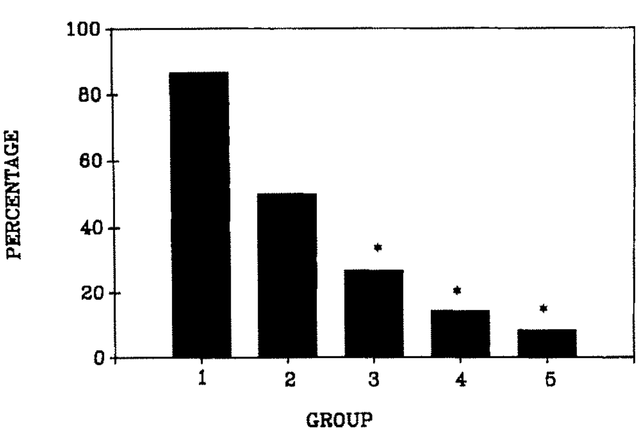

Figure 1. Percentage of each group with gastric pH <2.5 (*significantly different from placebo, $P < 0.05$).

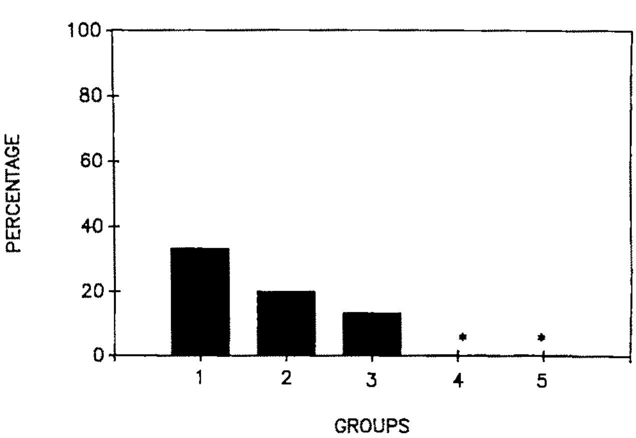

Figure 2. Percentage of patients with volumes >25 mL (*significantly different from placebo, $P < 0.05$).

when compared with placebo. All patients in these two groups had volumes <25 mL. However, there was no difference between control and groups 2 and 3 who took only one dose the night before. The actual numbers of patients with gastric volumes >25 mL are shown in Table 2. Figure 2 illustrates the percentage of patients in each group with gastric volumes >25 mL.

Time Intervals

No significant regression correlation between interval and pH was found when combining famotidine groups (2 and 4) or ranitidine groups (3 and 5). However, when combining both ranitidine groups (groups 3 and 5), ranitidine was found to be effective for up to 12 hr after ingestion.

Discussion

Aspiration pneumonitis secondary to gastric content regurgitation and aspiration is a recognized complication of anesthesia. This syndrome has been shown in animal studies to be associated with gastric volumes >25 mL (3) and a gastric pH <2.5 (2). Therefore, multiple agents have been tried in humans to decrease gastric acidity and gastric volumes in an attempt to decrease hypothetically the incidence of aspiration and severity of pneumonitis if aspiration does occur. These agents have included particulate antacids, nonparticulate antacids, anticholinergics, dopaminergic inhibitors (metaclopramide), and H_2-receptor antagonists cimetidine and ranitidine. However, the converse, gastric volumes <25 mL or gastric pH >2.5 has never been proved in humans to either decrease the frequency of pulmonary aspiration or decrease the intensity and magnitude of pneumonitis resulting from such aspiration.

The most recent addition to this armamentarium is famotidine (Pepcid/MSD), a new competitive H_2-receptor antagonist that is 30–100 times more potent than cimetidine and 3–20 times more potent than ranitidine (6). After oral administration, peak levels are obtained in 1–3 hr with antisecretory effects lasting up to 12 hr (6). The advantages of the new H_2 blocker were to improve safety and to prolong the duration of action when compared with cimetidine. Cimetidine, with an overall good safety record, has been implicated in causing multiple side effects with the most significant being hypotension, cardiac arrhythmias, cardiac arrest, central nervous system (CNS) disturbances, bronchoconstriction, and drug interactions with theophylline, warfarin, and phenytoin (5). Ranitidine has also been associated with CNS changes and some hepatotoxicity (5). Famotidine has a few reports (5) of CNS changes but is too new to have significant side effects evaluated. Famotidine with its prolonged duration of action and high therapeutic index appeared to be an attractive alternative to the other drugs available.

Our study reconfirmed previous work (7,10) showing that outpatients have a high gastric volume and a low gastric pH. Our gastric volumes were less than those reported by Ong (10) probably secondary to different quantification techniques. Our approach of measuring gastric aspirate may underestimate true gastric content as determined by dye dilution but allows comparison between groups.

Studies evaluating cimetidine (9) and ranitidine (7) have found both to be effective in reducing gastric volume and acidity preoperatively. All of these studies involve the use of either a PO, IM, or IV dose of the medication the morning of surgery. We initially assumed that famotidine, with its longer half-life, would offer prolonged protection over cimetidine or ranitidine and thus be amenable to a single dose the night before anesthesia. We were able to show that with a dose at night and one in the morning, famotidine was as effective as ranitidine in decreasing gastric volume and acidity.

The study showed that ranitidine, despite its shorter elimination half-life, appeared to have a significantly longer effect at decreasing gastric volume and gastric acidity, even up to 12 hr after administration. This is reflected in the lack of significant difference between the ranitidine groups when evaluating intervals of <12 hr. This is significantly longer than Francis (8) who reports up to 8.5 hr of protection. The additional protection, however, provided by the second dose in the AM would suggest the continued use of this regimen. The lack of prolonged protection with famotidine may represent different pharmacokinetic or pharmacodynamic responses in healthy surgical outpatients when compared with duodenal ulcer patients with high acid secretion.

In summary, we have shown that outpatients have a high gastric volume and a low gastric pH. A single dose of an H_2 blocker the night before surgery is inadequate to provide a prolonged decrease in gastric volume and acidity. An additional dose the morning of surgery to supplement the evening dose remains the optimal method to decrease gastric volume and acidity and hopefully provide some protection from aspiration pneumonitis.

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References

1. Simpson JY. The alleged case of death from chloroform. Lancet 1848;1:175.
2. Teabeaut JR. Aspiration of gastric contents: an experimental study. Am J Pathol 1952;28:51–67.
3. James CF, Modell JH, Gibbs CP, Kuck EJ, Ruiz BC. Pulmonary aspiration-effects of volume and pH in the rat. Anesth Analg 1984;63:665–8.
4. Ash ASF, Scheld HO. Receptors mediating some actions of histamine. H_2-receptors. Br J Pharmacol 1966;27:427–39.
5. Freston JW. Safety perspectives on parenteral H_2-receptor antagonists. Am J Med 1987;83:58–67.
6. McCullough AJ. A multicenter, randomized, double-blinded study comparing famotidine and ranitidine in the treatment of active duodenal ulcer disease. Am J Med 1986;81:17–24.
7. Manchikanti L, Colliver JA, Grow JB, Demeyer RG, Hadley CH, Roush JR. Dose-response effects of intravenous ranitidine on gastric pH and volume in outpatients. Anesthesiology 1986;65:180–5.
8. Francis RN, Kwik RSH. Oral ranitidine for prophylaxis against Mendelson's syndrome. Anesth Analg 1982;61:130–2.
9. Weber L, Hirshman CA. Cimetidine for prophylaxis of aspiration pneumonitis: comparison of intramuscular and oral dosage schedules. Anesth Analg 1979;58:426–7.
10. Ong BY, Palahniuk RJ, Cumming M. Gastric volume and pH in out-patients. Can Anaesth Soc J 1978;25:36–9.

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An Anaphylactic Reaction to Fibrin Glue

Leslie Newberg Milde, MD

Key Words: ALLERGY, FIBRIN GLUE. BLOOD, COAGULATION—fibrin glue.

Cryoprecipitated fibrinogen, or fibrin glue, is among the newest technologic advances in the control of persistent bleeding during surgery. It duplicates the process of the final stage of normal coagulation. Like epoxy, fibrin glue is prepared from two components, bovine thrombin and human fibrinogen, which, when combined, produce a clot. Fibrin glue has been used for sealing suture holes, especially at vascular anastomoses; for sealing large oozing surfaces common in plastic surgical reconstruction; for sealing tracheal or esophageal anastomoses (1); for sealing persistent air leaks from lung lacerations (2) or bronchopleural fistulae (3); for sealing porous vascular prostheses; for hemostasis after tooth extraction; for connecting bone grafts during reconstructive otologic procedures; and for reconstructive nerve grafting. In most instances, the fibrinogen component of fibrin glue is prepared specifically from blood components taken from the patient who is to receive it in order to avoid the risk of transmission of viral diseases. This requires anticipating surgery at least 2 days in advance so that autologous blood can be drawn and prepared. The fibrinogen obtained from the patient's plasma (1 mL for every 100 mL of whole blood) is not pure and may include other clotting factors such as Factor XIII, which is responsible for the formation of the final fibrin polymer and immunoglobulins. At the time of surgery this fibrinogen is then mixed with bovine thrombin to produce a clot. The clot adheres to the necessary tissues, bone, or nerve within seconds but is then slowly reabsorbed in approximately 10 days by fibrinolysis. In some instances fibrin glue may be prepared with fibrinogen from single donor fresh frozen plasma, or cryoprecipitate, or with fresh frozen plasma obtained from pooled homologous blood donations. This report describes an anaphylactic reaction to fibrin glue made from homologous fresh frozen plasma by a patient, later found to have IgA deficiency and a high titer of class-specific IgA antibodies.

Report of a Case

A 57-year-old male with a persistent bronchopleural fistula was scheduled for closure of the bronchopleural fistula with fibrin glue and obliteration of the left pleural cavity with latissimus dorsi muscle and pectoralis major muscle flaps. Previous surgeries included bilateral femoral artery bypass grafts; carotid endarterectomy; a left upper lobectomy for pneumonia with cavity formation, which was complicated by a chronic left bronchopleural fistula; lung decortication and attempted closure of the bronchopleural fistula with a serratus anterior muscle transfer; and an open bronchopleural window for persistent empyema and bronchopleural fistula. His past medical history included chronic obstructive lung disease and hypertension. During one previous surgery the patient had received blood intraoperatively after which he became hypotensive to a systolic blood pressure of 80 mm Hg and bradycardic to 45 beats/min. He was successfully treated with mephentermine and the rest of his perioperative course was uneventful. He was known to be allergic to intravenous (IV) contrast dyes. The patient's blood group was B, Rh positive, D positive. His routine medications included Bactrim for the chronic empyema and aspirin. All laboratory values were within normal limits. The patient received no premedication. Routine monitoring and IV and radial arterial catheters were placed preoperatively. Following induction of anesthesia with thiopental, and increasing concentrations of isoflurane in 50% nitrous oxide with spontaneous ventilation, the patient's trachea was intubated with a right-sided double lumen tube the position of which was confirmed by bronchoscopy. The right lung was mechanically ventilated and the left lung allowed to deflate. The surgery consisted of dissecting free latissimus

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dorsi and pectoralis major muscles, and covering the area of the bronchopleural fistula with autogenous tissue.

Fibrin glue was then made by mixing 1 mL cryoprecipitated fibrinogen with each 1 mL bovine thrombin. A total of 8 mL fibrin glue was used to cover thoroughly the bronchopleural fistula. The pectoralis major and lattisimus dorsi muscle flaps were then placed in the pleural cavity. During this time the patient's blood pressure, which had been 100 to 120 mm Hg systolic throughout the procedure, decreased to 70 mm Hg systolic, and the heart rate decreased to 45 beats/min. Two-lung ventilation with 100% oxygen was begun. The systolic blood pressure was unresponsive to fluid transfusion and multiple doses of ephedrine (total 50 mg) and atropine (total 0.8 mg) and further decreased to 50 mm Hg. The patient was then given 1 mg epinephrine and 300 mg $CaCl_2$ with prompt return of the blood pressure, and a continuous infusion of epinephrine was started to maintain the blood pressure. A gram of hydrocortisone was given. The electrocardiogram never demonstrated any changes suggestive of myocardial ischemia. A pulmonary artery balloon occlusion catheter was placed, which demonstrated a pulmonary artery occlusion pressure of 14 mm Hg and a cardiac output of 8.0 L/min. The high cardiac output and the normal filling pressures indicated that a very low systemic vascular resistance was the cause of the hypotension rather than myocardial depression or failure. The surgery was completed, and the patient was taken to the intensive care unit, where he required inotropic support (epinephrine) and mechanical ventilation for the next 12 hr. There was no further evidence of bleeding, and his subsequent recovery was uneventful.

Because it was suspected that the patient had developed an anaphylactic reaction to the fibrin glue, his blood was tested for a possible transfusion reaction. The patient was found to be IgA deficient and to have a moderately high level of class-specific anti-IgA antibodies, which could account for the anaphylactic reaction. It was recommended that the patient receive only blood products from IgA-deficient donors.

Discussion

Approximately one or two patients per 1000 experience anaphylactic transfusion reactions (4). Antigen–antibody reactions involving white cells or red cells of the ABO, Rh, Kell, and Kidd systems are the most common in clinical practice (4). Of allergic reactions to the immunoglobulins, the most common are to IgA, which comprises 15% of the circulating immunoglobulins (5). IgA is divided into two subclasses, IgA1 and IgA2, the latter subclass being divided into two allotypic determinants, A2m(1) and A2m(2) (5). Antibodies to human IgA have been recognized since 1968 (6). The antibodies to IgA are usually of the IgG immunoglobulin class (7). These antibodies form antibody–antigen complexes that fix complement and release fragments of complement components C3a and C5a. Leukotrienes, the slow reacting substances of anaphylaxis, are also generated, and they mediate the characteristic anaphylactic symptoms (4). IgE antibodies to IgA have also been demonstrated that can also cause anaphylactic reactions (8). Anti-IgG and anti-IgM antibodies are rarely, if ever, responsible for transfusion reactions (9). IgA antibodies have been divided into two groups: 1) class-specific anti-IgA antibodies found in patients who are totally deficient in IgA, and 2) anti-IgA antibodies of limited specificity (6). The incidence of IgA antibodies of limited specificity depends on the reference population. It is reported to occur in 2% of normal adults, in 15% of women who have recently given birth (10,11), and in 21% of patients who have had multiple tranfusions (6,12,13). If the incidence is defined by any measureable titer of anti-IgA antibody of limited specificity (<1/8), one study reported a 59% incidence in a healthy blood donor population of 1010 (9).

In a study of 73,569 healthy volunteer blood donors the frequency of totally absent IgA was reported to be 1:886 (14). IgA-deficient individuals have an increased incidence of asthma, atopy, recurrent respiratory infections, rheumatoid arthritis, lupus erythematosus, and other autoimmune diseases, although the majority are asymptomatic (4). The patient in this report was allergic to IV contrast dyes and had a long history of recurrent respiratory infections. Although his long smoking history most likely accounted for his chronic obstructive lung disease and lung cancer, his IgA deficiency could have contributed to his postoperative complications following his original lung lobectomy.

Prior exposure to an antigen is required to produce sensitization via the production of antibodies. Before the reported episode it was not known that this patient was IgA deficient. It is likely that during his previous surgeries he received homologous blood products that then sensitized him to subsequent exposure. Indeed, the hypotension he experienced during his previous surgery may have been a manifestation of a milder allergic reaction to IgA in the blood he received rather than a manifestation of blood loss as had been assumed.

The incidence of anaphylactic reactions to IgA in blood or blood products is reported to range from 1/20,000 (15) to 1/47,000 (10) and is much rarer than the reported incidence of IgA deficiency. The absence of reactions in a majority of the susceptible population remains unexplained. Allergic reactions to IgA vary in severity from skin rashes to fatal anaphylaxis (7,10). Patients with limited specificity antibodies to only a specific subclass or allotype of IgA usually develop less severe reactions such as urticaria or anaphylactoid symptoms (6). Patients with total IgA deficiency and class-specific IgA antibodies will develop more severe reactions. They become hypotensive, can develop flushing and rashes (1–3%), and may develop respiratory signs such as wheezing and cyanosis. Severe hypotension produced primarily by systemic vasodilation as evidenced by the low systemic vascular resistance was the only allergic manifestation of the patient in this report. This type of anaphylactic transfusion reaction can be caused by even small amounts (16) of any blood products containing IgA, including whole blood, packed cells, plasma, plasma protein fraction, commercial human gamma globulin, or immunoglobulins. The only blood components that can be safely administered to these patients are blood products from IgA-deficient donors or red blood cells washed sufficiently to remove all donor IgA proteins. Files of IgA-deficient donors are maintained by the American Association of Blood Banks Rare Donors File, the Irwin Memorial Blood Bank in San Francisco, the American National Red Cross in Washington, D.C., and the Canadian Red Cross in Toronto.

Treatment for an anaphylactic anti-IgA reaction includes stopping the transfusion, administering epinephrine, and replacing fluid to fill the enlarged intravascular space resulting from the generalized vasodilation.

References

1. Kram HB, Shoemaker WC, Hino ST, Chiang HS, Harley DP, Fleming AW. Tracheal repair with fibrin glue. J Thorac Cardiovasc Surg 1985;90:771–5.
2. Dresdale A, Rose EA, Jeevanandam V, Reemtsma K, Bowman FO, Malm JR. Preparation of fibrin glue from single donor fresh frozen plasma. Surgery 1985;97:750–5.
3. Glover W, Chavis TV, Daniel TM, Kron IL, Spotnitz WD. Fibrin glue application through the flexible fiberoptic bronchoscope: Closure of bronchopleural fistulas. J Thorac Cardiovasc Surg 1987;93:470–3.
4. Branigan EF, Stevenson M, Charles D. Blood tranfusion reaction in a patient with immunoglobulin A deficiency. Obstet Gynecol 1983;61:47–9S.
5. Strauss RA, Gloster ES, Schanfield MS, Kiltinger SP, Morgan BB. Anaphylactic transfusion reaction associated with a possible anti-A2m(1). Clin Lab Haematol 1983;5:371–7.
6. Vyas GN, Perkins HA, Fudenberg HH. Anaphylactoid transfusion reactions associated with Anti-IgA. Lancet 1968;2:312–5.
7. Leikola J, Koistinen J, Lehtinen M, Virolainen M. IgA-induced anaphylactic transfusion reactions: A report of four cases. Blood 1973;42:111–9.
8. Bucks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. N Engl J Med 1986;314:560–4.
9. Rivat L, Rivat C, Daveau M, Popartz C. Comparative frequencies of anti-IgA antibodies among patients with anaphylactic transfusion reactions and among normal blood donors. Clin Immunol Immunopathol 1977;7:340–8.
10. Pineda AA, Taswell HF. Transfusion reactions associated with anti-IgA antibodies: Report of four cases and review of the literature. Transfusion 1975;15:10–5.
11. Vyas GN, Levin AS, Fudenberg HH. Intrauterine isoimmunization caused by maternal IgA crossing the placenta. Nature 1970;225:275–6.
12. Schmidt AP, Taswell HF, Gleich GJ. Anaphylactic transfusion reactions associated with anti-IgA antibody. N Engl J Med 1969;280:188–93.
13. Wells JV, Buckley RH, Schanfield MS, Fudenberg HH. Anaphylactic reactions to plasma infusions in patients with hypogammaglobulinemia and anti-IgA antibodies. Clin Immunol Immunopathol 1977;8:265–71.
14. Vyas GN, Perkins HA, Yang Y-M, Basantani GK. Healthy blood donors with selective absence of immunoglobulin. A: Prevention of anaphylactic transfusion reactions caused by antibodies to IgA. J Lab Clin Med 1975;85:838–42.
15. Bjerrum OJ, Jersild C. Class specific anti-IgA associated with severe anaphylactic transfusion reactions in a patient with pernicious anemia. Vox Sang 1971;21:411–24.
16. Mollison PL, Engelfriet CP, Contreras M. Blood Transfusion in Clinical Medicine. 5th ed. London: Blackwell Scientific Publications, 1987:737–40.

Effects of Lidocaine, Succinylcholine, and Tracheal Intubation on Intraocular Pressure in Children Anesthetized with Halothane-Nitrous Oxide

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Key Words: ANESTHETICS, LOCAL—lidocaine. EYE, INTRAOCULAR PRESSURE. NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE

Both succinylcholine and tracheal intubation may increase intraocular pressure (IOP) in lightly anesthetized individuals (1,2). Controversy exists concerning the relative contributions of succinylcholine or intubation itself to the increase in IOP (2,3). Because increased IOP might further damage the eye with a perforating injury (1,3), several drugs to prevent or attenuate intraocular hypertension caused by succinylcholine and intubation have been evaluated, with mixed results. Lidocaine pretreatment has been utilized in at least four studies (3–6), with moderate success reported in one (6); most patients were adults and all were given thiopental for induction of anesthesia.

To our knowledge, there has been no pediatric study specifically assessing the efficacy of lidocaine pretreatment in diminishing the increase in IOP associated in adults with succinylcholine and subsequent intubation. Furthermore, there has been no such study in patients undergoing an inhalation induction. We studied children in whom anesthesia was induced with halothane and nitrous oxide (N_2O). In addition to evaluating lidocaine pretreatment in preventing a succinylcholine-induced increase in IOP, we determined the effects of either lidocaine alone or succinylcholine alone on IOP and separately measured the additional effects of intubation on IOP. Preextubation measurements were also made.

Methods

This study was approved by the Human Subjects Research Committee, and a consent form was signed by each parent/guardian. Participants consisted of 75 ASA physical status 1 outpatients aged 18 months through 7 years undergoing surgery to correct strabismus. All were premedicated orally 1 hr before surgery with 0.02 mg/kg of atropine, 0.8 mg/kg of promethazine, and 25 mg/kg of chloral hydrate. Subjects were randomly assigned (by sealed envelopes) to one of three groups, and anesthesia was induced with halothane and N_2O. When a light surgical plane of anesthesia had been reached (approximately 7 min after mask application), children assigned to group 1 were given intravenous (IV) lidocaine, 2 mg/kg, followed in 30 sec by a saline placebo; children in group 2 were given a saline placebo followed in 30 sec by IV succinylcholine, 1 mg/kg; and children in group 3 were given IV lidocaine, 2 mg/kg, followed in 30 sec by IV succinylcholine, 1 mg/kg. Laryngoscopy was performed approximately 75 sec following the second injection. All patients were hyperventilated for approximately 5 sec prior to laryngoscopy (necessary in group 1 to abolish inherent respiratory drive). To ensure as much uniformity as possible in the depth of anesthesia at the time of intubation, all inductions were performed by the same anesthetist, who was blinded to the drug sequence.

Using a Kowa hand-held applanation tonometer, one of two ophthalmologists, also blinded to the drugs administered, measured IOP five times in the right eye (Figure 1): 1) just prior to drug administration (baseline); 2) drug effect, 60 sec following the second injection, but before hyperventilation for laryngoscopy; 3) immediately after intubation; 4) 1 min later; and 5) immediately before extubation, before the return of the cough reflex. Because IOP can vary with P_{CO_2} (7), end-tidal CO_2 was adjusted (by

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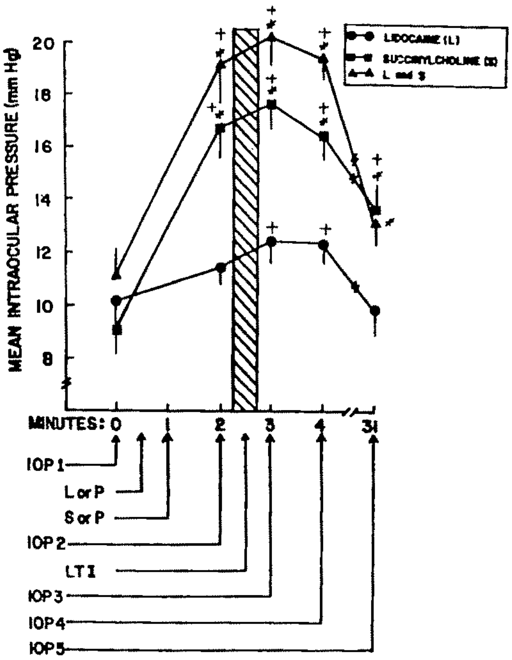

Figure 1. Diagram of the protocol sequence with intraocular pressures (mean ± SEM) in the three groups over time. Time 0 = approximately 7 min after anesthesia mask placement. Intraocular pressure (IOP) 1 = baseline; L or P = IV lidocaine, 2 mg/kg (L) or placebo (P); S or P = IV succinylcholine, 1 mg/kg (S) or placebo (P); IOP 2 = effect of drug(s); LTI = laryngoscopy and tracheal intubation; IOP 3 = postintubation; IOP 4 = 1 min after intubation; IOP 5 = before extubation. *$P < 0.01$ compared to lidocaine group (1). †$P < 0.05$ compared to baseline (group 1); $P < 0.01$ compared to baseline (groups 2 and 3).

varying ventilation) prior to IOP measurements 2 through 5 to remain within 7 mm Hg of that recorded at the time baseline measurements were made. During IOP measurements, no external pressure was placed on the orbit and there was no positive end-expiratory pressure (PEEP) in the anesthesia circuit.

Tabulated data included age, duration of anesthesia (from mask placement to arrival in the recovery room), and IOP measurements. Statistical significance ($P < 0.05$) was determined by one-way analysis of variance (ANOVA) for age and duration of anesthesia. The significance of differences between groups in IOP was tested with two-way analysis of covariance by repeated measures on the time variable, with baseline IOP measurement 1 used as a covariate. Effects of IOP over time within individual groups were evaluated by one-way ANOVA with repeated measures, utilizing the Newman–Keuls test for post-hoc analysis.

Results

There were no significant differences in age (mean ± SD of the three groups = 3.9 ± 1.8 years) and duration of anesthesia (44.1 ± 8.6 min).

Baseline IOP measurements were not significantly different in the three groups (Figure 1). The overall analysis of covariance, adjusted for baseline measures, demonstrated a significant interaction between time and the various groups ($P < 0.02$). This was due principally to the persistent significant increase in IOP above baseline levels at the fifth measurement in the succinylcholine-only group (2). Compared to the lidocaine-only group (1), IOP measurements 2 through 5 were significantly higher in both the succinylcholine-only (2) and in the combination (3) groups ($P < 0.01$). The administration of lidocaine 30 sec before succinylcholine (3) produced an additional increase in IOP measurements 2 through 4 that was not, however, statistically significant ($P < 0.07$) when compared to succinylcholine alone (2); the difference was minimal at IOP measurement 5 ($P < 0.51$).

Within the lidocaine-only group (1), there was no significant increase above baseline levels (IOP measurement 1) prior to intubation (IOP measurement 2), or change between before (IOP measurement 2) and after intubation (IOP measurement 3) levels; values after intubation (IOP measurements 3 and 4) were, however, slightly but significantly above baseline values. In both the groups given succinylcholine, either without (2) or with (3) lidocaine, their IOP measurements 2 (recorded after drug administration) were significantly increased over baseline levels. In all three groups, IOP increased <1 mm after intubation, but decreased slightly within 1 min following intubation. Just before extubation (IOP measurement 5), IOP in both groups given lidocaine (1 and 3) was not significantly different from baseline values, whereas IOP in patients in the succinylcholine-only group (2) remained significantly elevated over baseline values.

There were no complications associated with the IV bolus administration of 2 mg/kg of lidocaine during induction of anesthesia with halothane and N_2O. During the study period, heart rate and blood pressure remained within normal limits in all three groups, and there were no clinical signs (cough, lacrimation, dysrhythmias) to suggest an inadequate depth of anesthesia at the time of tracheal intubation.

Discussion

An increase in IOP associated with tracheal intubation may occur even in the absence of coughing and has been attributed to a reflex increase in sympathetic activity (2,8). Because lidocaine can attenuate hemodynamic reflex sympathetic responses to intubation (9), it might also be expected to reduce the increase in

IOP due to intubation. In children anesthetized with halothane-N_2O Drenger et al. (8) found that 2 min after IV administration of 2 mg/kg of lidocaine, but before intubation, there was a slight but statistically significant reduction in IOP compared to a placebo group, in which IOP actually increased prior to intubation. (Ventilatory patterns were not described.) Intubation was associated with significant increases in IOP in both groups, but the peak increase was significantly less with lidocaine. In contrast, our study showed that IOP had increased slightly 90 sec after IV administration of 2 mg/kg of lidocaine, but that there was no significant difference between IOP before and after intubation. However, we are in agreement that although IOP after intubation is significantly increased above baseline levels, the increase is minimal.

Increased IOP secondary to succinylcholine is thought to be primarily due to extraocular muscle contraction. Succinylcholine causes a sustained tonic contraction of slow fibers (1) in contrast to its paralytic effect on peripheral skeletal muscle following initial depolarization. Kaufman (10) demonstrated that the increase in muscle tension preceded respiratory paralysis and outlasted the period of apnea. The findings of our study are consistent with those of others who found that succinylcholine significantly increased IOP in children anesthetized with halothane-N_2O and that intubation did not significantly increase IOP further. Dear et al. (11) found that children given IV succinylcholine, 1 mg/kg, had significant (83%) increases in IOP, with intubation producing only an insignificant further 3% increase. In our study, IV succinylcholine, 1 mg/kg, resulted in an 84% increase in IOP, which increased another 5% upon insertion of the endotracheal tube. These results do not agree with the contention of Murphy et al. (3) that the increase in IOP secondary to succinylcholine is unimportant when compared to the rise secondary to intubation. Most likely, differences in induction techniques—IV versus inhalation—and differences in anesthetic depths at the time of intubation account for the discrepancy.

The rationale for the use of lidocaine to attenuate eye muscle contraction due to succinylcholine is derived from the observation that lidocaine reduces the incidence of succinylcholine-induced fasciculations and myalgia (12). To date, at least four studies (3–6) have evaluated lidocaine pretreatment to prevent increases in IOP caused by succinylcholine and/or tracheal intubation. Murphy et al. (3), Smith et al. (4), and Kruger and Roelofse (5) gave IV lidocaine in doses ranging from 1 to 2 mg/kg, administered 1 to 2 min before the administration of succinylcholine. All patients were given thiopental for induction of anesthesia. In two of the studies (4,5), postdrug (preintubation) IOP was not measured; baseline levels in both placebo and lidocaine groups were compared to IOP measurements after intubation. In the other study (3), preintubation pressures—measured <1 min following the administration of succinylcholine—were virtually unchanged from baseline and failed to reflect a succinylcholine-induced increase in IOP in either the placebo or lidocaine group. The authors of all three studies (3–5) concluded that lidocaine did not prevent an increase in IOP caused by succinylcholine and intubation; however, in our opinion, they did not properly assess the effect of the drugs alone on IOP without the additional effect of tracheal intubation on IOP. In contrast, Mahajan et al. (6), in measuring the effect of the drugs on IOP before intubation, demonstrated that IV lidocaine (1 mg/kg) significantly attenuated a succinylcholine-induced increase in IOP compared to placebo and prevented a further significant increase in IOP after intubation. In this study, lidocaine was given 5 min before the administration of thiopental and succinylcholine.

The results of the above study (6), when compared to our study, suggest that the efficacy of lidocaine pretreatment may depend upon the time between the administration of lidocaine and the administration of succinylcholine. We were unable to duplicate the timing of the drug sequence described by Mahajan et al. (6), as we do not routinely place an IV line in small children prior to induction. More studies are needed to confirm the interesting results of the study cited above, and to determine the optimal time interval between injections of lidocaine and succinylcholine in children.

Manipulation of the globe associated with eye muscle surgery may lower IOP to below baseline levels (13). In our study, only seven of the 75 children had no surgery in the right eye: two were in group 2 and four were in group 3. Therefore, we feel that the persistent significant increase in IOP over baseline levels in the succinylcholine-only group (2) after 30 min of anesthesia was truly indicative of residual eye-muscle contraction. The fact that levels of IOP with measurement 5 in the combination group (3) were not significantly above baseline values suggests that lidocaine exerted a late protective effect.

To summarize, in children undergoing induction of anesthesia with halothane and N_2O:

1) Lidocaine, 2 mg/kg IV, administered approximately 90 sec prior to laryngoscopy, results in a statistically insignificant increase in IOP, and there is no significant difference between IOPs measured immediately before and after tracheal intubation.

However, IOP after intubation is slightly but significantly increased above baseline levels.

2) Succinylcholine, 1 mg/kg IV, causes a significant increase in IOP 1 min after administration, and tracheal intubation produces no further significant rise. After 30 min of anesthesia, IOP is lower, but still significantly above baseline values.

3) Lidocaine, 2 mg/kg IV, administered 30 sec prior to succinylcholine, 1 mg/kg IV, does not prevent the increase in IOP associated with succinylcholine and may even enhance it to a small degree. However, lidocaine attenuates the persistent increase in IOP found 30 min after succinylcholine administration.

The authors wish to thank John Hayes (Coordinator of Research Information Systems for the Children's Hospital Research Foundation) for statistical analysis; David O. Warner, MD, for manuscript review; Larry Leguire, PhD, for the illustration; and Wendy Church, CRNA, for assistance with the study.

References

1. Lincoff HA, Breinin GM, DeVoe AG. The effect of succinylcholine on the extraocular muscles. Am J Ophthalmol 1957; 43:440–4.
2. Donlon JV. Anesthesia factors affecting intraocular pressure. Anesthesiol Rev 1981;8(Jan):13–8.
3. Murphy DF, Eustace P, Unwin A, Magner JB. Intravenous lignocaine pretreatment to prevent intraocular pressure rise following suxamethonium and tracheal intubation. Br J Ophthalmol 1986;70:596–8.
4. Smith RB, Babinski M, Leano N. The effect of lidocaine on succinylcholine-induced rise in intraocular pressure. Can Anaesth Soc J 1979;26:482–3.
5. Kruger AE, Roelofse JA. Precautions against intra-ocular pressure changes during endotracheal intubation—a comparison of pretreatment with intravenous lignocaine and diazepam. S Afr Med J 1983;63:887–8.
6. Mahajan RP, Grover VK, Munjal VP, Singh H. Double-blind comparison of lidocaine, tubocurarine and diazepam pretreatment in modifying intraocular pressure increases. Can J Anaesth 1987;34:41–5.
7. Samuel JR, Beaugié A. Effect of carbon dioxide on the intraocular pressure in man during general anaesthesia. Br J Ophthalmol 1974;58:62–7.
8. Drenger B, Pe'er J, BenEzra D, Katzenelson R, Davidson JT. The effect of intravenous lidocaine on the increase in intraocular pressure induced by tracheal intubation. Anesth Analg 1985;64:1211–3.
9. Tam S, Chung F, Campbell M. Intravenous lidocaine: Optimal time of injection before tracheal intubation. Anesth Analg 1987;66:1036–8.
10. Kaufman L. General anaesthesia in ophthalmology. Proc Roy Soc Med 1967;60:1275–80.
11. Dear GL, Hammerton M, Hatch DJ, Taylor D. Anaesthesia and intra-ocular pressure in young children. Anaesthesia 1987; 42:259–65.
12. Haldia KN, Chatterji S, Kacker SN. Intravenous lignocaine for prevention of muscle pain after succinylcholine. Anesth Analg 1973;52:849–52.
13. Pe'er J, Drenger B, BenEzra D. Intraocular pressure variation during strabismus surgery. J Pediatr Ophthalmol Strabismus 1986;23:98–100.

Letters to the Editor

"Just a Little Bit More"

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL.

To the Editor:

Several techniques are available for identification of entry of the tip of a needle into the epidural space (1–3). However, the tip of a needle may be in the epidural space, but it still may not be possible to pass a catheter through the needle into the space. When this difficulty is encountered, Bromage suggests advancing the needle "another half millimeter or so" to free the entire epidural needle opening from the ligamentum flavum (1). According to Moore (2) the epidural space may have been "tapped" if only 1⁄16 in. (0.15 cm) of the bevel of the needle has entered. The epidural catheter may well not pass through the bevel unless the entire opening of the bevel is in the epidural space. Moore advocates advancing the needle "1⁄16 in. (0.15 cm) to 1⁄8 in. (0.3 cm)" further into the epidural space (2). When following either of these methods, it is difficult to measure the exact distance when advancing the needle "another half millimeter" or "1⁄16 to 1⁄8 in." without a fixed reference point.

In gauging the distance of advancement of the epidural needle, one could use calibrated or scored needles (4,5). As these are not regularly available, we use as a marker the plastic collar that holds the needle within its sterile case to gauge the depth of the needle advancement when one is having difficulty advancing the catheter through the needle into the epidural space. By moving the marker to the point on the shaft equal to the distance we wish to advance the needle and advancing the needle until the marker contacts the skin, we will be assured of the proper increment. We then proceed to the usual confirmation maneuvers identifying the presence of the lumen of the needle in the epidural space.

In the event the plastic collar is inadvertently removed from the needle, we use a sterile marking pen to draw a line on the needle 0.5 cm or less from the skin. By this means we know exactly how far we have advanced the needle.

We have found the plastic collar to be an effective and useful maneuver when we want to advance the epidural needle "a little bit more" in advancing the catheter through the needle.

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References

1. Bromage PR. Identification of the epidural space. In: Epidural Analgesia Philadelphia: WB Saunders Co, 1989:176–214.
2. Moore DC. Continuous (intermittent) epidural (peridural) block. In Regional Block. Springfield: Charles Thomas Co, 1981:427–38.
3. Cousins MJ. Epidural neural blockade. In: Cousins MJ, Bridenbaugh PC eds. Neural Blockade. Philadelphia: JB Lippincott Co, 1980:176–274.
4. Lee JA. Specially marked needle to facilitate extradural block. Anaesthesia 1960;15:186.
5. Doughty A. A precise method of cannulating the lumbar epidural space Anaesthesia 1974;29:63.

Central Nervous System Effects of Magnesium

Key Words: IONS, MAGNESIUM.

To the Editor:

Thompson et al. (1) reported that hypermagnesemia significantly reduced the MAC of halothane anesthesia in rats. A subsequent letter (2) challenged the validity of the conclusion in part by stating that magnesium's effect on the central nervous system is relatively minor. We reported recently (3), however, that magnesium does in fact have a profound effect on spinal cord metabolism. Spinal cord glucose utilization was reduced 25–60% in rats at a plasma magnesium level of 13.5 ± 0.1 mEq/L. Although we did no measure the effect of magnesium on glucose utilization in brain, it seems reasonable to postulate a similar change Although a decrease in glucose utilization is not *a prior* evidence of an anesthetic or analgesic effect, the rate o glucose utilization does correlate with neuronal activity (4) Consequently, we believe it is inaccurate to state tha magnesium's effect on the central nervous system is minor

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References

1. Thompson SW, Moscicki JC, DiFazio CA. The anesthetic contribution of magnesium sulfate and ritodrine HCl in rats. Anesth Analg 1988;67:31–4.
2. Aldrete JA, Vazeery A. Is magnesium sulfate an anesthetic? (letter). Anesth Analg 1989;68:186–7.
3. Szabo MD, Crosby GJ. Effect of profound hypermagnesemia on spinal cord glucose utilization in rats. Stroke 1988;19:747–9.
4. Sokoloff L. Relation between physiological function and energy metabolism in the central nervous system. J Neurochem 1977;29:13–26.

Poststernotomy Neuralgia: A New Pain Syndrome

Key Words: PAIN, POST-STERNOTOMY. SURGERY, CARDIOVASCULAR.

To the Editor:

Three points of interest arise out of Drs. Defalque and Bromley's article (1).

First, all patients were men; presumably most were from a Veterans Administration Hospital, although the study began at Indiana University Medical Center. One wonders whether or not men have a lower pain threshold. Alternatively, the patient pool may have been all male.

Second, there was a 1- to 6-month delay in onset of this pain syndrome. Does this mean that the patients were preoccupied by other postoperative concerns in the interval and pain was not an issue? My impression is that neuroma pain in other scars becomes a problem soon after the wound heals.

Third, has this syndrome gone unrecognized and remains unrecognized (or at least not a problem) in my hospital's large cardiac surgery service of over 1000 patients per year?

One of the senior cardiac surgeons here believed that such discomfort is not a problem with us, although he could imagine that it might be among some patients with low pain thresholds. A second surgeon suggested a mechanism by which it might occur: spreading of the sternal retractor can, if applied strongly, buckle the costal cartilages. This is especially true with mammary artery grafts: 61% of the authors' patients had left internal mammary grafts and 63% had left sternal pain. Even so, this surgeon also agreed it was not a problem.

Finally, as director of our Anesthesia Pain Control Service over the entire period since cardiac surgery began, I have been asked to see only two patients with parasternal pain, to the best of my recollection.

I can only conclude that there must be a regional, surgical technical or a patient characteristic that selects this syndrome. Our patients are fortunate not to have found it to be a problem.

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Reference

1. Defalque RJ, Bromley JJ. Poststernotomy neuralgia: a new pain syndrome. Anesth Analg 69:81–2.

In Response:

We thank Dr. Todd for his interest. Almost all patients undergoing coronary artery bypass graft in our referring hospitals at the time of our study were men; about 75% of our patients were veterans.

The average time of onset of pain was 6 weeks. This is similar to the latency reported in another group of patients with postoperative neuromas (our reference 4). The pain of postoperative neuromas is probably caused by scar entrapment and the pain worsens as the scar contracts over the following weeks. Pinpointing the time of onset of chronic postoperative pain is difficult and may be affected by the previous use of analgesics and the patient's realization that his pain is increasing and has become chronic.

Dr. Todd's suggestion of chondral buckling as a cause of pain is interesting, but the well-defined, hard, exquisitely tender nodules that our probing needle found in the parasternal interspaces support the concept of a neuroma. There may, of course, be several causes of poststernotomy pain, including damage to bone or cartilage. Dr. Todd's suggestion that sternal retraction to harvest the left internal mammary artery would favor left-sided chondral buckling puzzles us.

We mentioned in our discussion that several surgeons and dolorologists had told us of seeing patients with parasternal pain after sternotomy and of obtaining good relief with repeated injections of bupivacaine with or without steroids.

The discrepancy between our findings and Dr. Todd's may be due to differences in surgical techniques, differences in patterns of patient referal and use of analgesics by cardiologists and surgeons, or regional differences in patients' stoicism. Our interest in the syndrome may have biased us toward a more aggressive search for patients with the type of pain we report so that we might more rapidly treat them.

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Book Reviews

Molecular and Cellular Mechanisms of Septic Shock, Progress in Clinical and Biological Research, Volume 286

B.L. Roth, T.B. Nielsen, A.E. McKee, eds. New York: Alan R. Liss, 1989, 316 pp, $58.00.

This book is an attempt to define the basic mechanisms responsible for both the metabolic and cardiopulmonary changes that occur during sepsis or endotoxemia. The book is a proceedings of a conference held in February 1988. Consequently, it contains a large amount of very current material. By and large the authors come to grips with many of the aspects of sepsis from the identification of endotoxin as a probable vector of gram-negative sepsis to the attempt to define a disruption of general membrane receptor and transport function as responsible for many of the pathophysiological changes noted.

The book is divided into three sections: one addresses receptors and signal transduction, another the role of endotoxin as a mediator, and the third cytokines and metabolic pathophysiology. The first section on receptor and signal transduction is a very excellent review of the latest developments in the area of calcium transport and its relationship to phospholipid physiology. Unfortunately this section suffers in many areas from the inordinate use of slang and abbreviations of terms, which make the text almost impossible to understand except by a specialist in the area.

The second section, which deals with endotoxin as a mediator of septic shock, has several excellent chapters, especially the one by Danner and Parrillo on endotoxin in human sepsis, which evaluates the therapeutic potential of lipid A analogs. The sections suffer, however, as several other authors, although writing interesting chapters, do not address the theme of the section. Especially noticeable is the absence of a discussion of bacterial translocation and its role in sepsis, as well as a discussion of endotoxin-like materials such as the proteoglycans produced by gram-positive organisms. In addition, there is almost no discussion of the possible mediators of lung injury and no discussion of renal changes. As these are very major areas of importance in sepsis, this may be a very serious defect.

The last section, on cytokines and metabolism, has an excellent review of the current material on tissue necrosis factor and interleukin-1. The important missing ingredient for this section is a review defining the metabolic lesions present in a clear and precise manner.

Although many of the hard hitters in the area of sepsis, especially those in the microvascular and the metabolic areas, are notably missing from this text, the text does give a very good description of many of the basic mechanisms that may be responsible for sepsis and is recommended reading for the anesthesiologist, especially for those working in intensive care situations.

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Surgery for Anaesthetists

John S. M. Zorab, ed. Boston: Blackwell Scientific Publications, 1988, 512 pp, $165.00.

Responding to a perceived need for anesthetists to understand surgical diseases and procedures better, Dr. Zorab and 36 British and Australian surgeons, anesthetists, and one physicist have labored long to provide us with this unique opus. In a format similar to texts on medicine for anesthetists the authors cover a wide range of topics—from the operating room and its special equipment, such as electrocautery and lasers, to details of adult and pediatric general and specialty surgery and associated medical conditions. Most of the 49 chapters are authored by teams of surgeons and anesthetists. The chapters vary greatly in providing pearls for the anesthetists, pertinent illustrations, and surgical principles.

Chapters providing a wealth of information are those on pediatric surgery, ophthalmology, gynecology, orthopedics, cardiothoracic surgery, plastic surgery, urology, and biliary surgery. Information on specific topics can be gleaned by consulting the table of contents or the 20-page index. Nothing is mentioned, however, regarding cesarean section surgery.

Because so few references are provided it is difficult for the reader to judge how up-to-date the chapters are or where to turn for further information. The newest reference cited was 1985. Little documentation is offered for the opinions provided by the chapter authors.

Who should purchase this textbook? Certainly large departmental or medical school reference libraries will find

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it of use for their patrons. With so many new texts and journals vying for our attention today probably few individual practitioners or trainees will have the funds or time to indulge their curiosity about what happens on the other side of the ether screen.

In conclusion, this comprehensive textbook on anesthetic aspects of surgery and surgical diseases offers new insights that may help us jointly to offer better, more complete care to our anesthetic-surgical patients. Hopefully, later editions of this book will contain more documentation and references to supplement and reinforce the opinions provided in such lucid detail by the editor and chapter authors. We realize this is not an easy task for busy volunteers to deliver promptly and succinctly.

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On Chloroform and Other Anaesthetics: Their Action and Administration

John Snow. London: John Churchill, 1858, 487 pp, $37.50. Third reprinting in 1989 by the Wood Library Museum of Anesthesiology, Park Ridge, Ill.

A reviewer can only approach John Snow's *On Chloroform and Other Anaesthetics: Their Action and Administration* with some trepidation. It is akin to being asked to review the Bible. To carry the analogy further, one can surmise that many have heard of both books, but far fewer have read them.

After studying this seminal work, one is struck by the acuity of the author's observations. This is the product of a highly methodical, analytical, and perceptive mind. The specialty of anesthesia is indeed fortunate that a person with the talents of John Snow was one of its pioneers.

On Chloroform and Other Anesthetics stresses the empirical basis of early anesthetic practice. However, Snow's approach is scientific. This is evidenced by his elucidation of the volumes of chloroform vapor produced at different temperatures. The reader will be struck by the continuing relevance of Snow's comments regarding clinical practice. The range and complexity of procedures performed under chloroform-mask anesthesia are a testimonial to his clinical skills. The periphery of the body was still the site of virtually all operations, but the anesthetized state permited a less aggressive approach, e.g., debridement instead of amputation. Attempts at intraabdominal procedures reulted in death.

Snow outlines 50 cases in which the administration of hloroform proved fatal. He provides evidence derived rom animal experimentation that this is due to the cardiotoxicity of excessive inspired chloroform concentrations. t is surprising to see the techniques of mouth-to-mouth ventilation, tracheostomy, endotracheal intubation, and lectrical stimulus of the heart used in the ensuing resusitative efforts.

Against the background of increasingly sophisticated monitoring, a plethora of pharmacological agents, and a cornucopia of clinical and scientific data, Snow's book is a stark reminder that the acumen of the anesthesiologist is the final bastion of reason and safety during the conduct of anesthetic care.

This reviewer urges all anesthesiologists to set aside a week or two and read this book. Few works serve to enhance one's appreciation of the obstacles overcome by the original practitioners of our specialty as much as this one.

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Risk and Outcome in Anesthesia

David L. Brown, ed. Philadelphia: Lippincott, 1988, 420 pp, $49.50.

Multiauthored texts tend to suffer from unevenness of emphasis and writing as well as confusion amongst the authors regarding the kind of end product desired. *Risk and Outcome in Anesthesia* is no exception.

Recent years have witnessed a plethora of articles and studies looking at outcome in anesthesia. Rather than looking at discrete physiologic and pathologic changes related to a particular anesthetic technique or monitoring modality, investigators are increasingly focusing on overall outcome. To add to the confusion, separating outcome related to anesthetic technique or anesthetic monitoring from outcome related to the kind of surgery done, surgical competence, and/or its swiftness is both philosophically and statistically difficult. This reviewer remains cynical about claims advocating one anesthesia technique over another, when neither the surgical technique nor the length of the operation is factored into the statistical analysis. Claims that anesthesia for open heart surgery can safely be performed without the use of pulmonary artery monitoring is a recent example of this.

The term "risk" is commonly understood to mean the likelihood of injury. It does not necessarily imply substandard care, but could. The terms risk and outcome are related but not identical.

The body of the text is divided into two sections: the first covers perioperative risk, the second perioperative outcome. Each chapter in the first section deals with a discrete organ system. These chapters are generally well written and comprehensively indexed. The chapters on hematologic and immune function, psychiatric function, and endocrine and renal function are particularly interesting and well written, and the chapter on pulmonary function has an excellent historical section. Unfortunately, most of the chapters lack a unified understanding of the concept of risk and meander off into discussions of techniques for a variety of conditions. These discussions, although interesting and well-written, do not serve the stated objective of the section, namely, an articulation of the risks of anesthesia on various organ systems.

The second section, perioperative outcome does a better job of sticking to the objectives stated. The chapters on anesthetic choice and critical care are particularly well written and thoughtful. The remainder of the chapters in this section again follow organ systems and are generally well written and indexed.

Risk and Outcome in Anesthesia represents an exciting challenge: how can one outline scientifically and document the risks that appertain to the administration of anesthesia, as well as examine outcome statistics and their alterability by different techniques of administration? The text has not fulfilled this mission consistently.

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Cardiac Monitoring Anesthesiology Clinics of North America, December 1988

Guest Edited by Paul G. Barash, Philadelphia, W.B. Saunders Co., 1988, 275 pp, $65.00 per year for four monographs.

It was a pleasure to review the final monograph of the 1988 quarterly, *Anesthesiology Clinics of North America*, for a number of reasons. First, together with its September 1988 mate, *Myocardial Ischemia and Perioperative Infarction*, this monograph will bring any library of cardiovascular anesthesia up to date. Second, in combination with the annual monographs sponsored by the Society of Cardiovascular Anesthesiologists (SCA), this monograph will enrich any personal library of cardiovascular anesthesia at a bargain price. Finally, this monograph contains a chapter on "Electrical Safety and Device Calibration" that clearly and succinctly (in 20 pp) reviews the basics of electricity and electrocution, hospital electronics and surgical electrocautery, and device calibration and troubleshooting. With clear tables and simple circuit diagrams featuring safely smiling or electrocuted stick figures, this chapter clearly interprets intraoperative electrical risks and clarifies line isolation. Too bad current National Fire Protection Association (NFPA) Guidelines for hospitals have removed requirements for line isolation transformers and monitors in ORs and ICUs in favor of safer isolated power sources—and just when I was beginning to understand current leaks and line isolation!

Other strong points of this monograph include an interesting chapter on the historical development of cardiovascular monitoring, a comprehensive chapter on preoperative monitoring featuring nuclear cardiac imaging, and strong elementary chapters on transesophageal two-dimensional and Doppler echocardiography. Basic chapters on noninvasive blood pressure, pulmonary artery, cardiac output, and pediatric cardiovascular monitoring comprise the body of the text. Interesting new submissions on monitoring coronary circulation, venous circulation, and right ventricular function complete the monograph.

The few weak points in this work include a penultimate chapter on the physiologic basis for cardiovascular monitoring that should have been a starter; duplicated submissions on perioperative electrocardiography in chapters 2 and 14; and the assignment of a chapter on new ideas in cardiac output monitoring to a recognized pioneer in intraoperative transesophageal echocardiography who, nonetheless, does a good job with the complexities of bioimpedance.

The 1988 year-end monograph on *Cardiac Monitoring* from the *Anesthesiology Clinics of North American* has few shortcomings, is current and concise, and should serve both the general and the cardiac anesthesiologist as a review source for classic cardiovascular monitoring and as an introductory source for two-dimensional echocardiographic and pulsed-Doppler flow monitoring.

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Anesthesia and the Lung

T. Stanley, R. Sperry, eds. The Netherlands: Kluwer Academic Press, 1989, 301 pp.

At the 34th Annual Postgraduate Course in Anesthesiology (Snowbird, Utah, February 17–21, 1989), an internationally renowned panel of contributors presented a wide range of topics in pulmonary medicine and respiratory pathophysiology, as well as a discussion of clinical and theoretical anesthetic issues. The Refresher Course manuscripts of these presentations have been reprinted in *Anesthesia and the Lung*. Although the sequence of chapters in the book probably follows the order in which the lectures had been presented, the chapters can be conceptually grouped into one of four categories.

The largest group of chapters covers new material or expands upon areas of pulmonary physiology relevant to anesthetic practice. A stimulating discussion of pulmonary endothelial cell biochemical activity is one example. A second group of chapters briefly covers several topics (e.g., effects of anesthetics on pulmonary gas exchange), providing the knowledgeable reader with guides to further specialized reading or a brief review. The third group of chapters reviews basic topics such as modes of mechanical ventilation and one-lung ventilation. These thoughtful reviews provide useful basic information with savvy clinical observations. Finally, a small portion of the book is devoted to historical coverage. Dr. Severinghaus briefly reviews the history of oximetry, and Dr. West discusses the 1981 expedition to Mt. Everest.

This text fulfills the editor's goal of providing a printed reference for the meeting's participants, and of rapidly disseminating the concepts presented. In addition, the text serves as a rapid review of and reference guide to recent developments in clinical aspects of anesthesia and the lung.

Unfortunately, the manuscripts are reprinted in their original fonts and styles. This production method permits the inclusion of occasional typographical errors and the presence of sketchy graphs with inadequate legends, which detract from the book's readability. Despite this shortcoming, *Anesthesia and the Lung* will be informative to both anesthesia residents and staff because of its timely coverage of both fundamental and esoteric principles of pulmonary pathophysiology.

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Cardiovascular Anesthesia and Postoperative Care (2nd edition)

S. Tarhan. Chicago: Yearbook Medical Publishers, 1989, 651 pp, $79.50.

The second edition of this text seeks to address the enormous expansion of knowledge which has occurred in cardiac anesthesiology since the first edition in 1982. The preface notes that new chapters have been added on anesthetic agents, pericardial disease, anesthesia for electrophysiologic testing and surgical treatment of arrhythmias, blood-related communicable diseases, and postoperative management. These join bread-and-butter cardiac anesthesia chapter topics such as preoperative evaluation, monitoring, and anesthetic management for valvular heart disease; ischemic heart disease; congenital malformations; pericardial disease; and thoracic aortic surgery. Adjunct topics of great interest to cardiac anesthesiologists such as pump oxygenators, myocardial preservation, brain protection, pacemakers, and circulatory assistance devices are also represented. Chapters on anesthetic management of abdominal aortic surgery and carotid surgery are included as well.

There is much in this text to praise. The contributors all practice or trained at the Mayo Clinic. As a result the text enjoys a unified viewpoint, in contrast to many other multiauthored texts. The authors also deserve praise for their liberal use of excellent graphics and tables. The illustrations in the chapter on anesthesia for surgical repair of pediatric congenital heart disease are particularly illuminating. Especially well-written and referenced are the chapters on anesthesia and pericardial disease and on anesthesia for thoracic aortic surgery.

The book is not without some deficiencies. Perhaps as all of the contributors stem from the same institution, there is an occasional tendency to sink to a "this is how we do it here" approach to a topic. This is evident in the chapter on oxygenators and hemodilution in cardiopulmonary bypass. The text seeks to address recent advances in cardiac anesthesia, but a chapter on anesthetic management of heart and heart-lung transplantation is conspicuous by its absence. Discussion of some esoteric topics such as anesthesia for patients with atrial myxomas and anesthesia for pulmonary thromboendarterectomy is likewise lacking.

Such criticisms should not overly detract from what is an otherwise excellent basic text of cardiac anesthesiology. It should find wide acceptance among trainees in cardiac anesthesia.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Baskett PJF, ed. *Cardiopulmonary Resuscitation*. Vol. 17 in Monographs in Anesthesiology. New York: Elsevier, 1989, 416 pp, $184.25.

Brisman R, ed. *Neurosurgical and Medical Management of Pain: Trigeminal Neuralgia, Chronic Pain, and Cancer Pain*. Boston: Kluwer Academic Publishers, 1989, 205 pp, $79.95.

Chung EK. *Principles of Cardiac Arrhythmias*, 4th ed. Baltimore: Williams and Wilkins, 1989, 835 pp, $119.95.

Hill CS Jr, Fields WS, eds. *Drug Treatment of Cancer Pain in a Drug-Oriented Society*. Vol. 2 in Advances in Pain Research and Therapy. New York: Raven Press, 1989, 380 pp, $86.00.

Passmore JC, ed. *Perspectives in Shock Research: Metabolism, Immunology, Mediators, and Models*. Vol. 299 of Progress in Clinical and Biological Research. New York: Alan R. Liss, Inc., 1989, 339 pp, $70.00.

Stoelting RK, Miller RD. *Basics of Anesthesia*, 2nd ed. New York: Churchill Livingstone, Inc., 1989, 523 pp, $31.95.

Scott DB. *Techniques of Regional Anesthesia*. E. Norwalk, Conn.: Appleton & Lange, 1989, 211 pp, $85.00.

Scott DB. *Introduction to Regional Anesthesia*. E. Norwalk, Conn.: Appleton & Lange, 1989, 94 pp, $24.00.

Thomas SJ, ed. *Diagnosis and Management of Arrhythmias*. Vol. 7, No. 2 of Anesthesiology Clinics of North America. Philadelphia: WB Saunders, June 1989, 224 pp, $69.00 annual subscription of four, or $28.00 per single issue.

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Anesthesia and Analgesia

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Contents

Volume 69, Number 6, December 1989

EDITORIALS

Regional Anesthesia for Pediatric Surgery	*D. B. Scott*	697
Fluid Resuscitation in Septic Shock: No Solution Yet	*Donald S. Prough and William E. Johnston*	699

SCIENTIFIC ARTICLES

Comparison of the Fascia Iliaca Compartment Block with the 3-in-1 Block in Children	*Bernard Dalens, Guy Vanneuville, and Alain Tanguy*	705
Hypertonic Saline Solution-Hetastarch for Fluid Resuscitation in Experimental Septic Shock	*Charles W. Armistead Jr, Jean-Louis Vincent, Jean-Charles Preiser, Daniel De Backer, and Thuc Le Minh*	714
Effects of Halothane on the Conduction System of the Heart in Humans	*Gert J. Scheffer, Remmet Jonges, H. Steele Holley, Cees A. Grimbergen, Henk H. Ros, Abraham Peper, and Leo H. D. J. Booij*	721
Effects of Parenteral Amino Acid Nutritional Regimens on Oxidative and Conjugative Drug Metabolism	*Eugene J. Pantuck, Charles Weissman, Carol B. Pantuck, and Young Joo Lee*	727
In Vitro Study on Mechanisms of Bupivacaine-Induced Depression of Myocardial Contractility	*Jean J. Eledjam, Jean E. de La Coussaye, Josep Brugada, Bruno Bassoul, Jean P. Gagnol, Juan R. Fabregat, Christian Massé, and Antoine Sassine*	732
Disposition Kinetics of Ropivacaine in Humans	*A. Lee, D. Fagan, M. Lamont, G. T. Tucker, M. Halldin, and D. B. Scott*	736
Motor and Sensory Blockade After Epidural Injection of Mepivacaine, Bupivacaine, and Etidocaine—A Double-Blind Study	*K. Axelsson, P-A. Nydahl, L. Philipson, and P. Larsson*	739
Delayed Side Effects of Droperidol After Ambulatory General Anesthesia	*Brian Melnick, Rita Sawyer, Deepa Karambelkar, Preyaratt Phitayakorn, Nonita T. Lim Uy, and Rita Patel*	748
Interaction Between Nondepolarizing Neuromuscular Blocking Agents and Inhalational Anesthetics	*Joseph Swen, Omar M. Rashkovsky, Jantine M. Ket, Henk W. J. Koot, Jo Hermans, and Sandor Agoston*	752
Fentanyl Inhibits the Canine Carotid Chemoreceptor Reflex	*Nikolaus Mayer, Michael Zimpfer, Gerhard Raberger, and Alexander Beck*	756
Preoperative Anxiety: Is It a Predictable Entity?	*Alice D. Domar, Laura L. Everett, and Myra G. Keeler*	763

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SCIENTIFIC ARTICLES—continued

Orientation of Fibers in Human Dorsal Lumbar Dura Mater in Relation to Lumbar Puncture — *B. Raymond Fink and Stuart Walker* — 768

Efficacy of Oral Cyclosporine Given Prior to Liver Transplantation — *Marc R. Brown, Dan Brajtbord, Dennis W. Johnson, Michael A. E. Ramsay, and A. William Paulsen* — 773

Serum Ammonia Levels in Response to Glycine Infusion in Normal and Cirrhotic Rats — *Edward J. Frink Jr, David A. DiGiovanni, John R. Davis, and Burnell R. Brown Jr* — 776

Passive or Active Inspired Gas Humidification Increases Thermal Steady-State Temperatures in Anesthetized Infants — *Bruno Bissonnette and Daniel I. Sessler* — 783

Intraneural Recording of Muscle Sympathetic Activity During Epidural Anesthesia in Humans — *Stefan Lundin, B. Gunnar Wallin, and Mikael Elam* — 788

Comparative Systemic Toxicity of Convulsant and Supraconvulsant Doses of Intravenous Ropivacaine, Bupivacaine, and Lidocaine in the Conscious Dog — *Hal S. Feldman, G. Richard Arthur, and Benjamin G. Covino* — 794

What Is the Safest Endotracheal Tube for Nd-YAG Laser Surgery?—A Comparative Study — *Mitchel B. Sosis* — 802

REVIEW ARTICLE

Role of Pulmonary Surfactant in the Development and Treatment of Adult Respiratory Distress Syndrome — *Bruce A. Holm and Sadis Matalon* — 805

CLINICAL REPORTS

Effect of Epinephrine on the Duration of Dibucaine (Cinchocaine) Spinal Anesthesia — *Robert E. Beavis* — 819

Adverse Responses Following Intraoperative Administration of Orthoclone OKT3 — *Steven Roth and Josh P. Kupferberg* — 822

Epidural Morphine Provides Greater Pain Relief Than Patient-Controlled Intravenous Morphine Following Cholecystectomy — *Keith A. Loper, L. Brian Ready, Michael Nessly, and Suzanne E. Rapp* — 826

Biphasic Carbon Dioxide Elimination Waveform with Right Mainstem Bronchial Intubation — *Dean Gilbert and Jonathan L. Benumof* — 829

Intraoperative Administration of the Intravenous Angiotensin-Converting Enzyme Inhibitor, Enalaprilat, in a Patient with Congestive Heart Failure — *Gregory A. Acampora, Jose A. Melendez, Deborah L. Keefe, Alan D. Turnbull, and Robert F. Bedford* — 833

Marked Sensitivity to Pancuronium in a Patient Without Clinical Manifestations of Myasthenia Gravis — *Taijiro Enoki, Yoshiyuki Naito, Yoshihiro Hirokawa, Ryoichi Nomura, Yoshio Hatano, and Kenjiro Mori* — 840

Inorganic Fluoride and Prolonged Isoflurane Anesthesia in the Intensive Care Unit — *Robert D. Truog and Susan A. Rice* — 843

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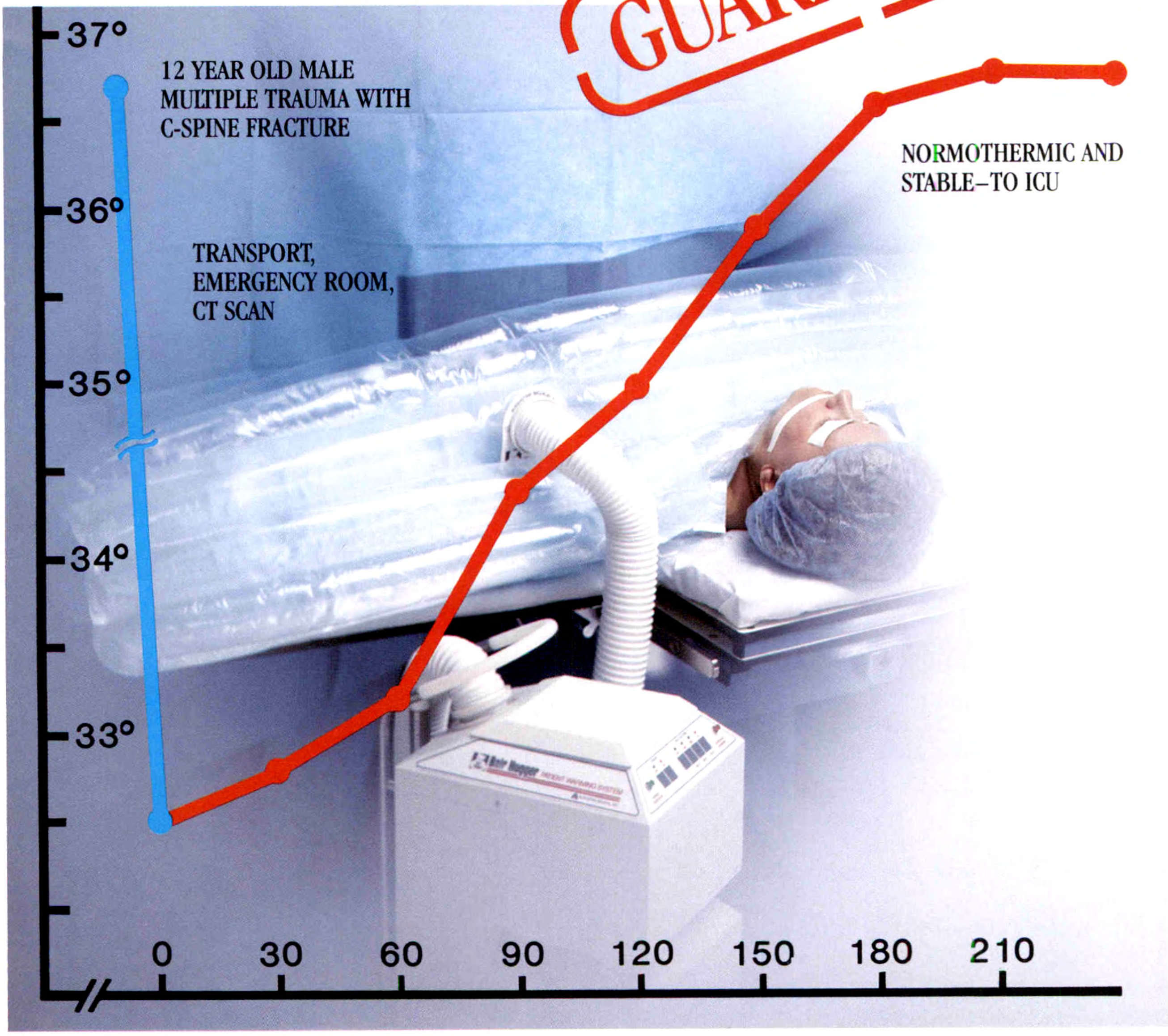

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CLINICAL REPORTS—continued

Isolated Postoperative Myoglobinuria in a Pediatric Outpatient. A Case Report of Malignant Hyperthermia — *Patrick K. Birmingham, George W. Stevenson, Tetsu Uejima, and Steven C. Hall* — 846

LETTERS TO THE EDITOR

Alfentanil Partition Coefficient — *David J. Stone and Cosmo A. DiFazio* — 850

The Beelzebub Nitrogen and Preoxygenation — *Chuck Biddle* — 850

In Response — *Mark C. Norris and Michael E. Goldberg* — 851

Pulse Oximeters — *Patricia R. Faubert* — 851

In Response — *Christian M. Alexander, Lynn E. Teller, and Jeffrey B. Gross* — 852

Lumbar Plexus Blocks and Lumbar Plexus Nerve Blocks — *Bernard Dalens, Alain Tanguy, and Guy Vanneuville* — 852

In Response — *Stephen K. Parkinson, James B. Mueller, William L. Little, and Steven L. Bailey* — 854

Coronary Artery Vasospasm Following Placement of a Cold Liver Graft During Orthotopic Liver Transplantation — *Michael A. E. Ramsay, Flavio Takaoka, Marc R. Brown, and Paul Rosenlöf* — 854

Inadvertent Benzyl Alcohol Administration in Neonates: Do We Contribute? — *Paul Reynolds and Niall Wilton* — 855

A Method of Securing Epidural Catheters — *Lester G. Schmitt and David A. Ullman* — 856

BOOK REVIEWS

Anesthesia — *Isaac Azar* — 858

Textbook of Pediatric Anesthetic Practice — *Robert C. Pascucci* — 859

Cardiopulmonary Bypass: Current Concepts and Controversies — *William A. Lell and A. J. Wright* — 859

Transplant Surgery: Anaesthesia and Perioperative Care (Volume 16, Monographs in Anaesthesiology) — *Yoogoo Kang* — 860

Guest Reviewers for 1989 — 861

Author Index — 864

Subject Index — 872

References: 1. Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stress associated with worse outcome? *Anesthesiology.* 1987;67:A1. Abstract. **2.** Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. *Anesthesiology.* 1986;65:A516. Abstract. **3.** de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. *Anesthesiology.* 1982;56:112-118. **4.** Flacke JW, Bloor BC, Kripke BJ, et al: Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: A double-blind study. *Anesth Analg* 1985;64:897-910. **5.** Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. *Anesthesiology.* 1987;66:130-135.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely.

Protect from light. Store at room temperature 15°-30° C (59°-86° F).

March 1986, March 1987
U.S Patent No. 3,998,834
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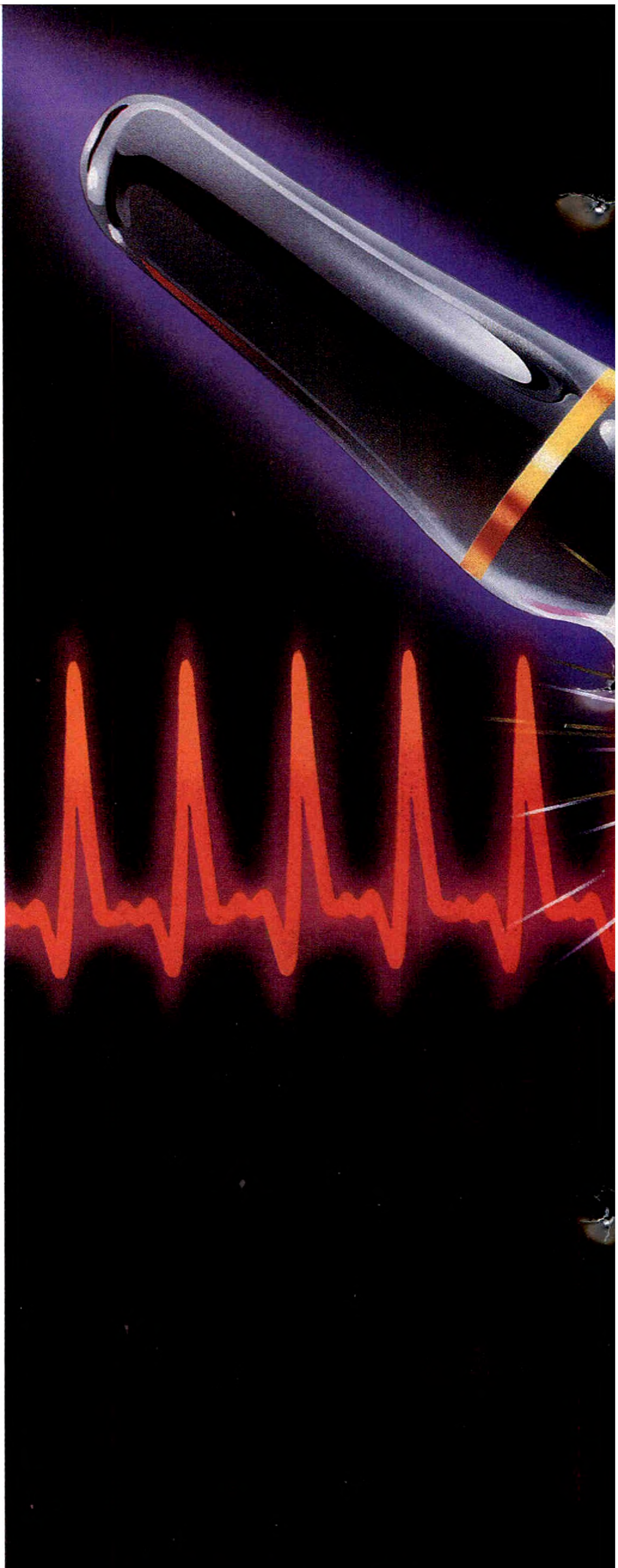

As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

Editorials

Regional Anesthesia for Pediatric Surgery

D. B. Scott, MD, FRCP, FFARCS

Key Words: ANESTHESIA, PEDIATRIC—regional. ANESTHETIC TECHNIQUES, REGIONAL—pediatric.

Until recent years, regional anesthesia has not been widely used in pediatric anesthesia. Performing operations on conscious children could not be justified in most circumstances. However, the use of balanced techniques that combine regional anesthesia with light general anesthesia in adults has been increasing. The advantages are many and include a smooth operative course as painful stimuli are prevented from reaching the central nervous system, a considerable modification of the surgical stress response, and excellent analgesia in the early postoperative period. Unlike techniques that use muscle relaxants, there is no need to use controlled ventilation (unless it is specifically indicated). There is no valid reason why children should not benefit from these advantages.

Whereas using regional anesthesia during surgery has many advantages, some anesthesiologists are more impressed with the postoperative analgesia and elect in many circumstances to inject the local anesthetic after surgery ends (1). There is little doubt that a child awakening without pain is much easier to manage than one who wakes with pain. Although the effect of the local anesthetic will wear off eventually, there is sufficient time in most cases to administer an analgesic to a rational and cooperative patient when pain appears.

Children are far from being a homogeneous group, varying as they do from tiny premature neonates to quite large adolescents. The psychological approach to each patient must, of course, vary enormously. A neonate can be given a spinal or caudal anesthetic and remain awake with the simple aid of a comforter (2), there having been no previous experience of fear. Even premature infants do well with this technique, which would raise eyebrows (and even hands in horror) in more conventional circles (3–5). Looked at cooly, however, the use of general anesthesia in such cases is not exactly straightforward and devoid of risk (6,7).

As the child grows and becomes dependent emotionally on its parents, the whole approach must be different if unnecessary distress is to be avoided. In most cases, general anesthesia must be induced before proceeding to the regional block (8). In adults, many experts prefer to perform the more major blocks with the patient awake, the main advantage being the preservation of patient cooperation, e.g., in determining the result of a test dose, reporting parasthesia, or detecting early symptoms of toxicity. These advantages must be foregone in children but they are seldom paramount (9).

Because of the changes in physiology that occur as a child grows, there are important differences in the effects produced by central nerve blocks (spinal and epidural). Even very high blocks cause little or no change in blood pressure or heart rate up to the age of about 6 yr (10). The physiological adaptation to the hydrostatic pressure changes brought about by posture and height are very underdeveloped because such adaptation is unnecessary in small individuals. Hypotension requiring treatment is rare and there is little or no circulatory perturbation (11). Postspinal headache is also uncommon. On the converse side, spinal anesthesia is of much shorter duration in babies than that in older children or adults (10), presumably because they have a different pattern of cerebrospinal fluid formation and circulation.

Epidural blockade, usually by the sacral approach, has become very popular chiefly because it is technically quite easy compared with the case with adults. The sacral hiatus is easy to palpate and the sacral

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canal is usually entered without difficulty. Catheter techniques with both the caudal and lumbar approaches are becoming commonplace. Prolonged analgesia with and without the aid of epidural opioids is then possible (9).

The more "perfect" anatomy of children compared with that of adults (particularly the elderly) greatly facilitates the performance of peripheral nerve and plexus blocks. Considerable technical success can be achieved with lumbosacral and brachial plexus blocks, although the use of a nerve stimulator is a wise precaution if direct trauma to a nerve or an intraneural injection is to be avoided. Special needles and catheters for use in children are available or being developed.

Minor nerve blocks [such as ileoinguinal and genitofemoral after hernia repair (12,13) or intercostal block after thoractomy (1)], local infiltration of the incision, and even topical anesthesia can all be used to good effect in preventing postoperative pain. The effort required is minimal as are the risks.

More major nerve blocks in children, however, are more controversial. Some anesthesiologists are concerned that blocks such as the three-in-one and sciatic nerve block for lower limb surgery or brachial plexus block are unnecessarily invasive in children. Of course, blocks should not be performed because like Mt. Everest, they are there. There must be some rationale for their use that has advantages over simpler techniques, such as epidural or spinal block or indeed general anesthesia by itself. However, it is irrational to consider that children will receive fewer benefits than adults from these more complicated procedures, provided a benefit can be clearly defined. Major peripheral blocks provide more localized anesthesia than the central blocks and their physiological effects are much less. Although children tolerate the effects of sympathetic blockade very well, they are nevertheless still liable to have bilaterally paralyzed lower limbs in the early postoperative period, and an accidental intrathecal injection given during an attempted caudal block can produce apnea and unconciousness. In extensive and prolonged surgery of the upper limb (e.g., replantation of a severed digit), the simplicity of the light general anesthesia required with a brachial plexus block has advantages. Moreover, by maintaining the block postoperatively (with a catheter), the arm can be made analgesic, immobile, and sympathectomized.

A good example of the recent attention being paid to major regional anesthesia in children is the article in this issue of *Anesthesia and Analgesia* by Dalens et al. (14) in which they describe their use of an alternative to the three-in-one block of Winnie. Although at first sight such blocks may appear overly aggressive, the authors found their method simple, effective, and without complications. Indeed, this may well represent future developments and advances in pediatric anesthesia.

Needless to say, like many situations in medicine in general and anesthesia in particular, training and constant usage are of the essence. The best anesthetic for a patient is the one you give best. However, if we leave mental "road blocks" in place, such as the idea that major peripheral blocks are never justified in children, we will be quite unable to perform them when the indication is compelling. Those responsible for teaching must try to impart knowledge of a wide variety of anesthetic methods and not concentrate on producing anesthesiologists with tunnel vision. If children are to receive the maximal benefits during and after surgery, then all forms of anesthesia, including regional anesthesia, both major and minor, must be considered and employed where appropriate.

References

1. Shelly MP, Park GR. Intercostal nerve blockade for children. Anaesthesia 1987;42:541–4.
2. Arthur DS. Caudal anaesthesia in neonates and infants. Anaesthesia 1980;35:1136–7.
3. Abajian JC, Mellish RWP, Browne AF, Perkins FM, Lambert DH, Mazuzan JE. Spinal anesthesia for surgery in the high-risk infant. Anesth Analg 1984;63:359–62.
4. Harnik EV, Hoy GR, Potolicchio S, Stewart DR, Siegelman RE. Spinal anesthesia in premature infants recovering from respiratory distress syndrome. Anesthesiology 1986;64:95–9.
5. Gallagher TM, Crean PM. Spinal anaesthesia in infants born prematurely. Anaesthesia 1989;44:434–6.
6. Steward DJ. Preterm infants are more prone to complications following minor surgery than are term infants. Anesthesiology 1982;56:304–6.
7. Tiret L, Nivoche Y, Hatton J, Desmonts JM, Vouc'h G. Complications related to anaesthesia in infants and children. A prospective survey of 40,240 anaesthetics. Br J Anaesth 1988; 61:263–9.
8. Armitage EN. Regional anaesthesia in paediatrics. Clin Anaesthesiol 1985;3:553–68.
9. Dalens B. Regional anesthesia in children. Anesth Analg 1989;68:654–72.
10. Dohi S, Naito H, Takahashi T. Age related changes in blood pressure and duration of motor block in spinal anesthesia. Anesthesiology 1979;50:319–23.
11. Broadman LM, Hannallah RS, Norden RS, McGill WA. "Kiddie caudals:" experience with 1154 consecutive cases without complications. Anesth Analg 1987;66:S18.
12. Smith BAC, Jones SEF. Analgesia after herniotomy in paediatric day unit. Br Med J 1982;285:1466.
13. Markham SJ, Tomlinson J, Hain WR. Ilioinguinal nerve block in children—a comparison with caudal block for intra and postoperative analgesia. Anaesthesia 1986;41:1098–103.
14. Dalens B, Vanneuville G, Tanguy A. Comparison of the fascia iliaca compartment block with the 3-in-1 block in children. Anesth Analg 1989;69:705–13.

Fluid Resuscitation in Septic Shock: No Solution Yet

Donald S. Prough, MD and William E. Johnston, MD

Key Words: SHOCK—septic. FLUID BALANCE, COLLOID—hydroxyethylstarch. FLUID BALANCE, CRYSTALLOID—hypertonic saline.

In this issue, using a model of experimental endotoxic shock, Armistead and colleagues report that 6.0% hydroxyethylstarch in hypertonic (7.5%) saline improves blood pressure, cardiac output, and myocardial contractility in comparison to 6.0% hydroxyethylstarch in 0.9% saline (1). For two reasons, their results represent an important contribution to the growing literature on hypertonic resuscitation fluid. First, few investigators have applied hypertonic resuscitation techniques to models of septic shock. Second, Armistead and colleagues have compared not only the acute hemodynamic effects of resuscitation but also the influence of the two fluids on subsequent fluid requirements.

Several issues merit discussion if the conclusions of the authors are to be placed in proper perspective. The first issue is whether 6.0% hydroxyethylstarch in 7.5% saline, or any similar fluid, is likely to provide substantial advantages over conventional crystalloid and colloid fluids. The second issue, suggested by the authors' simulation of a clinical fluid resuscitation sequence, is the choice of an appropriate physiologic end point for ongoing fluid administration in shock states. The third issue, arising from an apparent salutary effect of the hypertonic combination on left ventricular performance, is the accurate evaluation of changes in myocardial contractility in an intact animal.

The need for an alternative to conventional crystalloid and colloid fluids for acute resuscitation is apparent from even a cursory review of the advantages and disadvantages of current fluid choices (Table 1). An ideal alternative would be inexpensive, produce minimal peripheral or pulmonary edema, and generate sustained hemodynamic effects. In addition, the value for resuscitation of civilian or military trauma victims would be enhanced if the solution were effective even if administered in smaller volumes than conventional fluids (2). Based upon data gathered during the past decade, hypertonic salt solutions appear to fulfill some of these criteria.

Although basic and clinical investigators have studied various hypertonic resuscitation solutions for much of this century (3–10), current enthusiasm results from work published by Velasco and colleagues in the *American Journal of Physiology* in 1980 (11). They reported the effects of 7.5% saline (6.0 mL/kg) as the sole resuscitative measure in lightly anesthetized dogs that had been subjected to sufficient hemorrhage (averaging 23 ± 2.1 mL/kg) to reduce mean arterial pressure (MAP) to 45–50 mm Hg for 30 min. Hypertonic saline restored systolic blood pressure and cardiac output and increased mesenteric blood flow to greater than control values. The most striking observation was that cardiac output and mesenteric blood flow remained stable for 6 h, after which time the animals were killed. In an accompanying survival study, 100% of a group of animals that had undergone slightly greater hemorrhage survived after infusion of 4.0 mL/kg of 7.5% saline (11). Although posttreatment serum osmolality exceeded 330 mOsm/L, no animal showed adverse effects attributable to acute hypertonicity (11). Preliminary data suggested similar efficacy in humans (12). In animals, the mechanism of hemodynamic improvement appeared to be a reflex response mediated by the arrival of a highly hypertonic mixture in the pulmonary circulation. Infusion into the aorta or into vagally blocked animals failed to produce comparable improvement (13) as did infusion into the pulmonary artery of a surgically denervated lung (14).

Subsequent investigations, extending experimental observations that began in the early 1900s (3,4), demonstrated the potential advantages of hypertonic resuscitation solutions on intracranial hemodynamics. Intracranial pressure increased during resuscitation from hemorrhagic shock with lactated Ringer's

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Table 1. Colloid vs Crystalloid: Reported Advantages and Disadvantages

Solution	Advantages	Disadvantages
Crystalloid	Inexpensive Promotes urinary flow Restores third space losses	Peripheral edema Pulmonary edema[a] Transient hemodynamic effects
Colloid	Sustained plasma volume increase Smaller volume required Lower intracranial pressure[a] Less peripheral edema	Expensive Coagulopathy (dex > HES) Pulmonary edema in capillary leak states Decreased Ca^{2+} (alb) Renal failure (dex) Osmotic diuresis Impaired cross-match (dex)

Alb, albumin; dex, dextran; HES, hetastarch.
[a]Represents concepts that remain controversial.

solution but remained unchanged if 7.5% saline was infused in a sufficient volume to comparably improve systemic hemodynamics (15,16). Todd and colleagues compared 0.9% saline to hypertonic lactated Ringer's solution (252 mEq/L Na^+) in anesthetized rabbits and demonstrated that the hypertonic solution maintained a lower intracranial pressure after isovolemic hemodilution (17). Zornow and colleagues subsequently quantified the reciprocal relationship between brain water and acute changes in plasma osmolality (18).

Unfortunately, in most animal models, improvements in systemic hemodynamic values, unlike those reported by Velasco and colleagues (11), have not been sustained. Prough and colleagues reported an initial improvement followed by a rapid decline in blood flow and cardiac output after resuscitation with either lactated Ringer's solution or hypertonic saline in pentobarbital-anesthetized dogs (16). Both 7.5% saline (6.0 mL/kg IV) and lactated Ringer's solution (60 mL/kg IV) improved MAP and cardiac output immediately following resuscitation after 30 min of hemorrhage to a MAP of 40 mm Hg (16). However, in the ensuing 60 min, both variables rapidly declined. In a canine model of oleic acid-induced pulmonary edema, Johnston and colleagues administered 7.5% saline (5.0 mL/kg IV) and noted a prompt increase in cardiac output and systolic and diastolic pressures, despite a statistically insignificant increase (1.0 mm Hg) in pulmonary artery occlusion pressure (PAOP) (19). However, the improvement had largely disappeared 30 min after injection. Armistead and colleagues demonstrated that the acute improvements in MAP, cardiac output, and left ventricular stroke wave (LVSW) associated with the hypertonic combination solution had greatly diminished by 60 min after infusion, despite continued maintenance of PAOP with additional fluid (1). The transient effects of hypertonic saline administration represent a major obstacle to wider clinical application. Possible strategies that might prolong the therapeutic effects beyond 30–60 min include a continued infusion of hypertonic saline, subsequent infusion of blood or of conventional fluids (as done by Armistead and colleagues), or modification of the original hypertonic solution.

Investigators have modified hypertonic saline solutions in an effort to exert more sustained effects while maintaining the advantages of hypertonic resuscitation. Jelenko and colleagues resuscitated burn patients by adding albumin to a solution containing 240 mEq/L of Na^+ (6). Smith and colleagues developed a solution similar to that tested by Armistead et al. by adding 6.0% Dextran 70 to 7.5% saline, and increased the duration of hemodynamic improvement when compared with equal volumes of hypertonic saline, sodium bicarbonate, or sodium chloride/sodium acetate (20). Currently, the combination of 6.0% Dextran 70 in 7.5% saline is undergoing clinical trials to determine its clinical applicability as the initial intravenous infusion in patients who have suffered civilian blunt or penetrating trauma.

With the exception of fluid resuscitation for burn wounds (6–8), the clinical implications of hypertonic resuscitation remain unclear because most preclinical studies have compared the effects of single boluses of experimental and control fluids. Although such a design may duplicate acute field resuscitation after military or civilian trauma, routine clinical fluid resuscitation rarely consists of a single bolus; rather, it continues until clinical signs indicate that no additional fluid is required. If single boluses of equal volumes of fluids of markedly differing tonicity are compared, the results of the comparison are predictable. Therefore, in the study by Armistead and colleagues, 10.0 mL/kg of 6.0% hydroxyethylstarch in 0.9% saline should fail to produce hemodynamic effects equivalent to 10.0 mL/kg of 6.0% hydroxy-

Table 2. Possible End Points for Comparison of Resuscitation Fluids

End point	Advantages	Disadvantages
Equal volume	Simple calculation	Different acute effects Different time-course
Equal sodium load	Simple calculation	Different acute effects Different time-course
Equal preload (i.e., CVP, PAOP)	Simple, continuous measurement	Determined by multiple, simultaneously changing variables
Equal cardiac output	Simple measurement, can be frequently repeated	Misleading if fluids differentially affect hemoglobin concentration
Equal oxygen delivery	Logical, physiologically appealing end point	Difficult calculation to make frequently; calculated from two simultaneously changing variables
Equal oxygen consumption	Physiologically reasonable	Difficult calculation to make frequently; calculated from two simultaneously changing variables

CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure.

ethylstarch in 7.5% saline (1). An alternative comparison, the infusion of equal quantities of Na^+ or equal numbers of osmoles dissolved in different volumes of water, will probably show that the larger volume exerts the greater immediate hemodynamic effect. In either case, it is necessary to continue observation into the postresuscitation period. Furthermore, it is preferable to continue fluid administration, as clinical shock would require ongoing fluid infusion.

An attempt to simulate the clinical situation necessitates a choice among a variety of possible goals of resuscitation. Armistead and colleagues chose to continue resuscitation with conventional crystalloid, using maintenance of PAOP at baseline values as an end point (1). Pulmonary artery occlusion pressure reflects the interaction of multiple variables, including blood volume, venous capacitance, left ventricular (LV) afterload, LV diastolic compliance, and LV contractility. Consequently, comparison of two or more resuscitation regimens that alter more than one variable may generate misleading conclusions; in addition, comparisons between reports may be rendered virtually impossible. For example, because hypertonicity reduces systemic vascular resistance (a physiologic effect that failed to attain statistical significance in Armistead's study), PAOP should also decline as systolic ventricular ejection becomes more complete; theoretically, therefore, more fluid would be necessary to restore a filling pressure similar to that produced by hydroxyethylstarch alone. Conversely, if hypertonicity-induced venoconstriction reduced the size of the capacitance bed, as suggested by Velasco and colleagues (11), a given blood volume should produce a greater PAOP. Therefore, the observation that hypertonic solutions do not reduce the volume of fluid required after the initial bolus may apply only if PAOP is used as the goal of resuscitation.

More physiologically sophisticated goals, also based on invasive monitoring, have been proposed. Shoemaker and colleagues have recently suggested that resuscitation of high-risk surgical patients to quantitative, prospectively defined measurements of systemic oxygen delivery ($\dot{D}o_2$) improves outcome in comparison to less rigorous goals (21). A predetermined level of $\dot{D}o_2$ is a theoretically attractive end point for resuscitation. It combines in a single term cardiac output and arterial oxygen content (Cao_2) according to the equation:

$$\dot{D}o_2 = \text{cardiac output} \cdot Cao_2 \cdot 10.$$

However, because asanguineous fluid resuscitation both increases cardiac output and decreases hemoglobin concentration, the application of $\dot{D}o_2$ as a goal poses practical difficulties. For example, Johnston and colleagues, in the study noted above (19), demonstrated an acute 70% increase in cardiac output after infusing hypertonic saline in animals with oleic acid-induced pulmonary edema. Because the increase in cardiac output greatly exceeded the acute 12% decline in hemoglobin concentration, $\dot{D}o_2$ increased. As the effects on cardiac output dissipated, however, the hemoglobin remained lower than preinfusion levels, resulting in a small decline in $\dot{D}o_2$ from preinfusion levels. Despite the straightforward arithmetic implications of simultaneous increases in cardiac output and decreases in Cao_2, most clinicians attempt to increase cardiac output (whether or not it is directly measured) as a goal during rapid volume expansion. Alternative end points for resuscitation are outlined in Table 2.

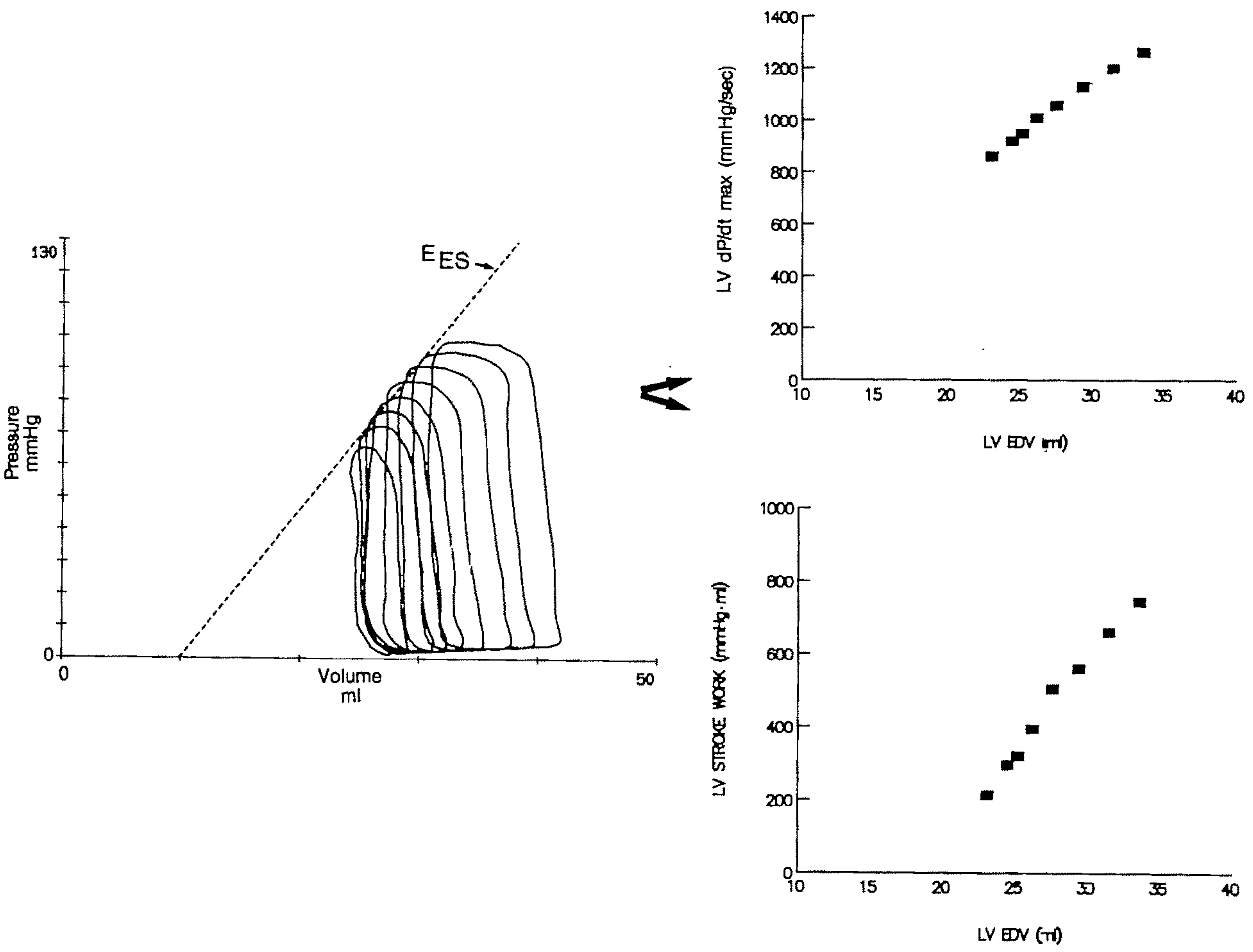

Figure 1. Example of generation of pressure-volume loops in an anesthetized dog. During bicaval occlusion, left ventricular (LV) pressure and volume steadily decline to generate a range of variably loaded pressure-volume loops. The slope of a line, termed end-systolic elastance or E_{ES}, connecting the end-systolic pressure-volume points, represents a sensitive indicator of myocardial contractile function. In addition, using data obtained from the LV pressure-volume loops, LV dP/dt_{max} and LVSW can be compared with LV end-diastolic volume (LV EDV). The slopes and volume axis intercepts of these relationships represent load-insensitive indices of contractile function. With myocardial depression, these relationships are shifted downward, causing a decrease in the slope values, whereas with enhanced contractile function, these relationships are shifted upward, causing an increase in slope values.

Based on increases in LVSW, Armistead and colleagues suggest that hypertonic solutions improve LV contractility in endotoxic shock. If so, this observation requires experimental and clinical correlation. Despite the relatively high cardiac output commonly present in human sepsis, myocardial contractility may be severely depressed (22). The reported beneficial effects of hypertonicity on myocardial performance are varied and include augmentation of preload (by volume expansion and reflex venoconstriction), increased LV contractility, and reduction of afterload (11). However, further interpretation of a positive effect on LV inotropy is difficult due to the inherent complexity of the relationship between PAOP and LVSW. First, LVSW is a measurement of external work performed by the heart, not of myocardial contractility per se. Second, the relationship between PAOP and LVSW is not linear but curvilinear. The curvilinear relationship reaches a plateau at elevated filling pressures because of the exponential nature of the diastolic pressure-volume curve (11), i.e., at greater diastolic ventricular volumes, further increments in LV end-diastolic volume produce large increases in LV end-diastolic pressure. In contrast, a linear relationship exists between LVSW and LV end-diastolic volume (11).

Armistead and colleagues reported that 6.0% hydroxyethylstarch in 7.5% saline apparently improved LVSW in comparison with 6.0% hydroxyethylstarch in 0.9% saline at a similar level of PAOP during the initial fluid resuscitation. This observation could result from enhanced LV contractility, decreased LV afterload, or improved LV diastolic compliance. If, as the authors postulated, hypertonic saline were to

Table 3. Hypertonic Resuscitation Fluids: Advantages and Disadvantages

Solution	Advantages	Disadvantages
Hypertonic crystalloid	Inexpensive Promotes urinary flow Small initial volume Improved myocardial contractility Arteriolar dilation Reduced peripheral edema Lower intracranial pressure	Hypertonicity Precipitation of subdural hematoma Transient effect
Hypertonic crystalloid plus colloid (in comparison to hypertonic crystalloid alone)	More sustained hemodynamic response Reduced subsequent volume requirements	Added expense of colloid Coagulopathy (dex > HES) Accelerated loss in capillary leak states Decreased Ca^{2+} (alb) Renal failure (dex) Osmotic diuresis Impaired cross-match (dex) Hypertonicity

Alb, albumin; dex, dextran; HES, hetastarch.

improve diastolic compliance, then LV end-diastolic volume could increase without changing PAOP. If so, the apparent shift could have resulted solely from preload augmentation by the Frank–Starling mechanism, especially as initial ventricular filling pressures were low. The relative contributions from increased inotropy or afterload reduction cannot be differentiated using this technique.

The relationship between PAOP and LVSW, like other conventional means of measuring LV contractility, is highly sensitive to changes in loading conditions. Precise quantification of the hemodynamic effects of hypertonic saline in septic shock would require using a load-insensitive index to interpret any direct effect on myocardial performance. Recently, three such load-insensitive measures of LV contractile performance have been proposed using LV pressure-volume loops. These are the slopes and volume axis intercepts of the LV end-systolic pressure-volume relation (E_{ES}) (23), of the LV dP/dt_{max}-end-diastolic volume relation (24), and of the LVSW-end-diastolic volume relation (Figure 1) (25). These indices require the accurate determination of LV volume over a wide range of variably loaded beats, such as those generated during acute caval occlusion, but are ideal for assessing LV contractile performance as they are insensitive to loading conditions (26,27). A decrease in myocardial contractility (i.e., produced by global ischemia or β-adrenergic blockade) causes a downward shift of these relations. In contrast, a steeper slope occurs in response to increased LV contractile performance. Further research should investigate the response of one or more of these indices to hypertonic saline in endotoxic shock.

Will anesthesiologists and intensivists routinely use hypertonic or combination hypertonic/hyperoncotic fluids for resuscitation in the future? At present, there is no clear answer. Burn resuscitation is the only established clinical use of hypertonic resuscitation solutions. Pending further preclinical work, the theoretical advantages of such fluids appear attractive in the acute resuscitation of hypovolemic patients who have decreased intracranial compliance (16) (Table 3). Armistead and colleagues provide tantalizing evidence that hypertonic saline may transiently improve blood pressure, cardiac output, and myocardial contractility in experimental septic shock. If the effects on myocardial contractility can be confirmed using more sensitive measures in animal models of sepsis, hypertonic solutions deserve further study as adjunctive therapy in the acute stabilization of patients in septic shock.

References

1. Armistead CW Jr, Vincent J-L, Preiser J-C, De Backer D, Le Minh T. Hypertonic saline solution-hetastarch for fluid resuscitation in experimental septic shock. Anesth Analg 1989; 69:714–20.
2. Maningas PA, DeGuzman LR, Tillman FJ, et al. Small-volume infusion of 7.5% NaCl in 6% Dextran 70 for the treatment of severe hemorrhagic shock in swine. Ann Emerg Med 1986; 15:1131–7.
3. Weed LH, McKibben PS. Experimental alteration of brain bulk. Am J Physiol 1919;48:531–8.
4. Wilson BJ, Jones RF, Coleman ST, Moyer CA. The effects of various hypertonic sodium salt solutions on cisternal pressure. Surgery 1951;30:361–6.
5. Baue AE, Tragus ET, Parkins WM. Effects of sodium chloride and bicarbonate in shock with metabolic acidosis. Am J Physiol 1967;212:54–60.
6. Jelenko C III, Williams JB, Wheeler ML, et al. Studies in shock and resuscitation. I. Use of a hypertonic, albumin-containing, fluid demand regimen (HALFD) in resuscitation. Crit Care Med 1979;7:157–67.

7. Monafo WW, Chuntrasakul C, Ayvazian VH. Hypertonic sodium solutions in the treatment of burn shock. Am J Surg 1973;126:778–83.
8. Monafo WW. The treatment of burn shock by the intravenous and oral administration of hypertonic lactated saline solution. J Trauma 1970;10:575–86.
9. Liang C, Hood WB Jr. Mechanism of cardiac output response to hypertonic sodium chloride infusion in dogs. Am J Physiol 1978;235:H18–22.
10. Shackford SR, Sise MJ, Fridlund PH, et al. Hypertonic sodium lactate versus lactated Ringer's solution for intravenous fluid therapy in operations on the abdominal aorta. Surgery 1983; 94:41–51.
11. Velasco IT, Pontieri V, Rocha e Silva MR Jr, Lopes OU. Hyperosmotic NaCl and severe hemorrhagic shock. Am J Physiol 1980;239:H664–73.
12. DeFelippe J Jr, Timoner J, Velasco IT, Lopes OU, Rocha e Silva M. Treatment of refractory hypovolaemic shock by 7.5% sodium chloride injections. Lancet 1980;8:1002–4.
13. Lopes OU, Pontieri V, Rocha e Silva MR Jr, Velasco IT. Hyperosmotic NaCl and severe hemorrhagic shock: role of the innervated lung. Am J Physiol 1981;241:H883–90.
14. Younes RN, Aun F, Tomida RM, Birolini D. The role of lung innervation in the hemodynamic response to hypertonic sodium chloride solutions in hemorrhagic shock. Surgery 1985; 98:900–6.
15. Prough DS, Johnson JC, Poole GV Jr, Stullken EH, Johnston WE Jr, Royster R. Effects on intracranial pressure of resuscitation from hemorrhagic shock with hypertonic saline versus lactated Ringer's solution. Crit Care Med 1985;13:407–11.
16. Prough DS, Johnson JC, Stump DA, Stullken EH, Poole GV Jr, Howard G. Effects of hypertonic saline versus lactated Ringer's solution on cerebral oxygen transport during resuscitation from hemorrhagic shock. J Neurosurg 1986;64:627–32.
17. Todd MM, Tommasino C, Moore S. Cerebral effects of isovolemic hemodilution with a hypertonic saline solution. J Neurosurg 1985;63:944–8.
18. Zornow MH, Todd MM, Moore SS. The acute cerebral effects of changes in plasma osmolality and oncotic pressure. Anesthesiology 1987;67:936–41.
19. Johnston WE, Alford PT, Prough DS, Howard G, Royster RL. Cardiopulmonary effects of hypertonic saline in canine oleic acid-induced pulmonary edema. Crit Care Med 1985;13:814–7.
20. Smith GJ, Kramer GC, Perron P, Nakayama S, Gunther RA, Holcroft JW. A comparison of several hypertonic solutions for resuscitation of bled sheep. J Surg Res 1985;39:517–28.
21. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988; 94:1176–86.
22. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984;100:483–90.
23. Kass DA, Maughan WL. From "Emax" to pressure-volume relations: a broader view. Circulation 1988;77:1203–12.
24. Little WC. The left ventricular dP/dt_{max}-end-diastolic volume relation in closed-chest dogs. Circ Res 1985;56:808–15.
25. Glower DD, Spratt JA, Snow ND, et al. Linearity of the Frank–Starling relationship in the intact heart: the concept of preload recruitable stroke work. Circulation 1985;71:994–1009.
26. Johnston WE, Vinten-Johansen J, Santamore WP, Case LD, Little WC. Mechanism of reduced cardiac output during positive end-expiratory pressure in the dog. Am Rev Resp Dis (in press).
27. Little WC, Cheng Che-Ping, Mumma M, Igarashi Y, Vinten-Johansen J, Johnston WE. Comparison of measures of left ventricular contractile performance derived from pressure-volume loops in conscious dogs. Circulation (in press).

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Comparison of the Fascia Iliaca Compartment Block with the 3-in-1 Block in Children

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DALENS B, VANNEUVILLE G, TANGUY A. Comparison of the fascia iliaca compartment block with the 3-in-1 block in children. Anesth Analg 1989;69:705–13.

A new single injection procedure, the fascia iliaca compartment block, is described for blocking the femoral, lateral cutaneous, and obturator nerves. The technique consists of injecting a local anesthetic immediately behind the fascia iliaca at the union of the lateral with the two medial thirds of the inguinal ligament, and forcing it upward by finger compression. This block was prospectively evaluated in 60 pediatric patients aged 0.7 to 17 years undergoing surgery of the lower limb, and then compared with a similar group of 60 children given a 3-in-1 block. Adequate analgesia was only obtained in 20% of the patients given 3-in-1 blocks (group 1), whereas the fascia iliaca compartment block proved to be easy, free of complications, and effective in more than 90% of patients (group 2). Such a high failure rate in group 1 was not due to misplacement of the needle since a femoral nerve block developed in all patients. Therefore it is unlikely that the local anesthetic can spread rostrally towards the lumbar plexus then return peripherally along the issuing nerves, and this was, indeed, not confirmed by radiological findings. In the authors' opinion, a multieffective block can only develop when the local anesthetic is introduced behind the fascia iliaca, which circumscribes a potential space where the femoral, lateral cutaneous, and obturator nerves run for a considerable part of their course. This report shows that deliberately injecting this space almost always results in an easy and effective block of these three nerves. The fascia iliaca compartment block can be recommended for use in children.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—lumbar plexus block, femoral nerve block. ANESTHESIA, PEDIATRIC.

The intraoperative and postoperative courses of numerous operations on the upper extremity are improved by using regional anesthetic techniques, especially axillary and supraclavicular brachial plexus blocks. The same improvements can be expected for operations on the lower extremity. However, due to the complexity of the sensory supply to the lower limb, either a central block or multiple peripheral blocks are necessary for providing adequate anesthesia. On the one hand, epidural or spinal anesthesias are unnecessary and even undesirable for unilateral operations; on the other, the performance of several peripheral blocks is time-consuming and increases the dangers of inaccurate injection and systemic toxicity.

Winnie et al. (1) renewed general interest in regional anesthesia for operations on the lower extremity by describing a multieffective block of the lumbar plexus nerves supplying the thigh with a singl injection of reasonable amounts of local anesthetic the "3-in-1" block. In a number of patients, howeve the block fails to provide adequate anesthesia in area supplied by the lateral cutaneous nerve of the thig and the obturator nerve. Furthermore, this bloc procedure has not gained wide acceptance in pedia rics, since most children are unable to grasp th concept of paresthesia. We expected that the use o electrical stimulation and insulated needles migh allow the application of the 3-in-1 block procedure i children, and even with improved results, but thi was not confirmed by our clinical experience.

We then reevaluated the gross anatomy of th lumbar plexus nerves and fascias of the groin an thigh in children. Our anatomical findings supporte the hypothesis that sufficient amounts of a solutio injected immediately posterior to the fascia iliac could spread at the inner surface of this fascia an contact the femoral, lateral cutaneous, genitofemoral and obturator nerves that run, at least in part, imme diately posterior to the fascia. We then developed new blocking procedure, referred to as the "fasci

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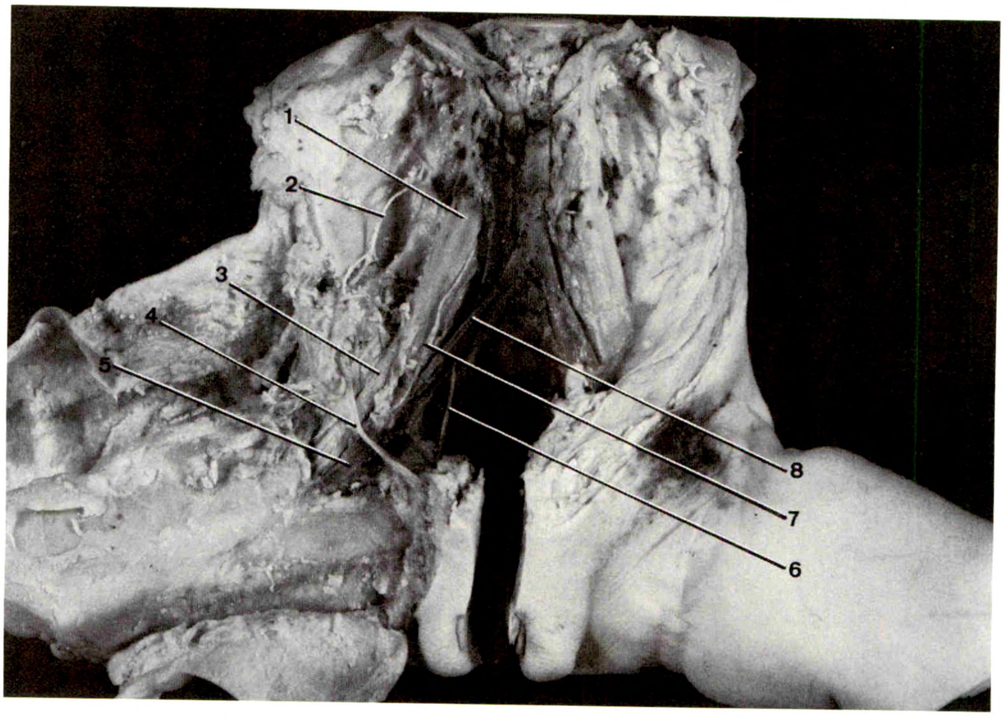


Figure 1. Gross anatomy of the lumbar plexus nerves supplying the lower extremity.

1. Psoas muscle
2. Lateral cutaneous nerve of the thigh
3. Femoral nerve
4. Inguinal ligament
5. Femoral vessels (within their specific sheath)
6. Obturator nerve
7. Genitofemoral nerve
8. Iliac vessels

iliaca compartment'' block. The present study was designed to evaluate prospectively the efficacy and reliability of this new technique and to compare it with the 3-in-1 block procedure in 120 pediatric patients. The study protocol received institutional approval as well as informed consent from parents. To reduce interindividual factors, all blocks were performed by the same anesthesiologist.

Material and Methods

Anatomic Considerations

The lower extremity is supplied by three nerves originating from the lumbar plexus which lies in the psoas compartment (3), within the substance of the psoas muscle. The *lateral cutaneous nerve of the thigh* (a sensory nerve) emerges at the upper part of the lateral border of the psoas muscle (Figure 1). It obliquely crosses the iliacus muscle, immediately posterior to the fascia iliaca, passes behind (or through) the inguinal ligament, and then divides into two terminal branches, which supply sensory innervation to the lateral aspect of the thigh. The *femoral nerve* (a mixed nerve) also emerges at the lateral border of the psoas muscle, runs posterior to the fascia iliaca in the groove formed by the psoas with the iliacus muscles, passes behind the inguinal ligament, and then enters the groin in the femoral triangle lateral to the femoral vessels (Figure 1). It supplies both sensory innervation to the ventral aspect of the thigh and the periosteum of the femur and motor innervation to the muscles of the front of the thigh. The *obturator nerve* (mixed, but mainly a motor nerve) emerges at the medial border of the psoas muscle (Figure 1), behind the common iliac vessels, from which it is separated by the fascia iliaca. It then reaches the obturator foramen, where it divides into two terminal branches that are then distributed to the thigh. An accessory obturator nerve may occasionally accompany the obturator nerve.

Two other lumbar plexus nerves also contribute sensory fibers to the upper part of the anterior aspect of the thigh: 1) the *ilioinguinal nerve*, which emerges at the lateral border of the psoas muscle, then crosses the quadratus lumbarum muscle obliquely, immediately posterior to its covering fascia until it reaches the iliac crest, where it pierces the transversus abdominis and the oblique muscles in the direction of the spermatic cord (in the male) or the round ligament of the uterus (in the female); and 2) the *genitofemoral nerve*, which perforates the psoas muscle, then runs on its anterior aspect (Figure 1), posterior to the fascia iliaca, in the direction of the inguinal ligament, where it divides in two terminal branches, genital and femoral, the latter supplying sensory innervation to the skin covering Scarpa's triangle.

Thus, the femoral, lateral cutaneous, obturator, and genitofemoral nerves run a considerable part of their course close to the inner aspect of the fascia iliaca. This complex fascia (3) is attached medially to the vertebral column and the upper part of the sacrum (Figure 2). Rostrally, it covers the psoas muscle and blends laterally with the fascia covering the quadratus lumbarum muscle. Caudally, it covers the iliacus muscle and is tightly attached to the inner lip of the iliac crest, and, medially, to the pelvic brim. The external iliac vessels are anterior to it, whereas the lumbar plexus nerves are posterior to it. At the groin, the fascia iliaca is continuous with the posterior margin of the inguinal ligament. Medially, it passes behind the femoral vessels (which are enclosed in a common sheath limiting a perivasculary space often referred to as the *lacuna vasorum*) and blends with the pectineal fascia which attaches to the pecten pubis (Figure 3). At this level, it also derives fibers towards the capsule of the hip: these fibers form a septum, usually incomplete, which reinforces the division between the femoral nerve (wrapped in its specific sheath) and the lacuna vasorum within which run the femoral vessels.

More caudally, at the level of the femoral triangle the fascia iliaca becomes narrow. Laterally, it attaches to the anterior superior iliac spine and then blends with the fascia covering the sartorius muscle. Medially, it is continuous with the pectineal fascia. It is covered by the fascia lata and it forms the roof of a fat-filled space, sometimes referred to as the *lacuna musculorum* (adjacent to the lacuna vasorum).

Finally, the fascia iliaca delimits a potential space, the "fascia iliaca compartment," triangular in shape (Figure 2). The limits of this compartment are:

1) anteriorly, the inner aspect of the fascia iliaca, which covers the iliacus muscle and reflects medially, thus covering the dorsal, then lateral, then ventral, and then medial aspects of the psoas muscle;
2) posteriorly, the outer aspect of the iliacus muscle;
3) medially, the vertebral column and the upper part of the sacrum; and
4) rostrally and laterally, the inner lip of the iliac crest to which the fascia is tightly attached (rostrally and medially, the space is continuous with that comprised between the quadratus lumbarum muscle and its covering fascia).

Below the inguinal ligament this space is continuou with the lacuna musculorum, covered by the fasci iliaca, the fascia lata, and then the skin covering th femoral triangle. Injecting a sufficient amount of solution in the lacuna musculorum and favoring it upward migration towards the iliacus muscle shoul result in a spread of the solution within the entir fascia iliaca compartment, thus allowing all the structures (especially the nerves) traversing this space t be contacted by the solution.

Patients

One hundred twenty patients, 78 males and 42 females, were included in this study after informe consent had been obtained from parents and, as ofte as possible, from the children themselves. The patients ranged in age from 0.7 to 17 years and i weight from 7.3 to 79 kg. They all underwent surger of the lower extremity, including 43 emergency procedures (Table 1). They were randomly allocated t one of two equal groups differing from one another i the blocking procedure used: 3-in-1 block in the 6 patients of group 1, and fascia iliaca compartmen block in the 60 patients of group 2.

Methods

Anesthetic methods. All procedures were carried ou in operating rooms after insertion of a periphera venous line. Twenty-six patients were kept alert an were given no drugs other than local anesthetics Children given general anesthesia in addition t regional anesthesia were given 0.02 mg/kg atropin and 0.1 mg/kg diazepam; as usual in our pediatri unit (4,5), anesthesia was then induced using eithe halothane in 35% O_2/65% N_2O or intravenous thiopental (4 mg/kg) as preferred by the patients, an maintained using halothane 0.25% to 0.5% in 35 O_2/65% N_2O.

Two needles connected to a plastic extension catheter ("immobile" needles [6]) were used: 1) 50-mm long 22-gauge insulated needles (Top needles) i group 1, and 2) 50-mm-long 24-gauge short beve needles (Plexufix from Braun) in group 2. A nerv stimulator (Myotest from Datex), adjusted to deliver mA impulses every second, was used in all patient in group 1. All patients were given the same anesthetic solution consisting of a mixture of 1% lidocain with 0.5% bupivacaine, both with 1:200,000 epinephrine. The volumes of local anesthetic injected wer

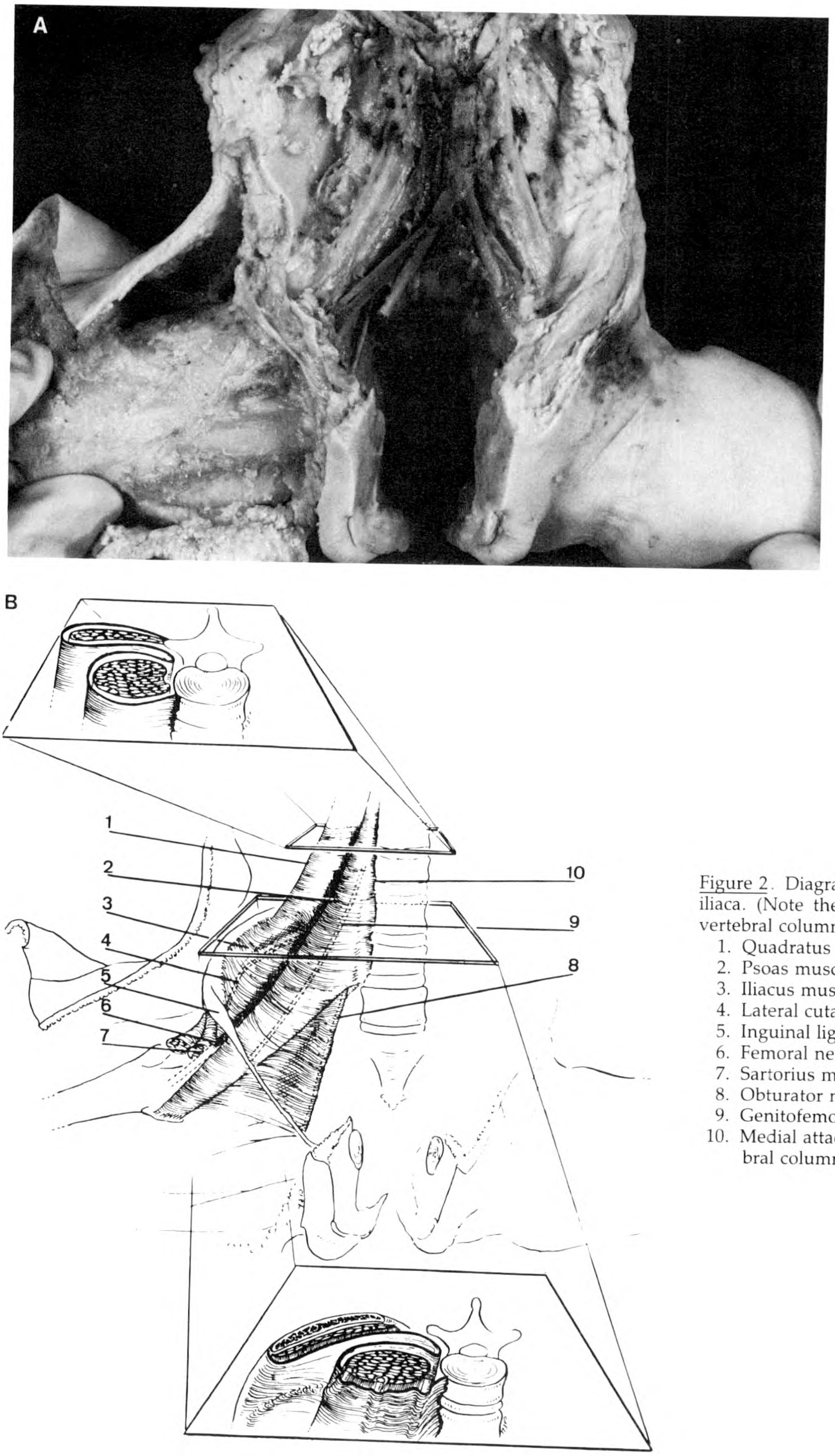


Figure 2. Diagrammatic representation of the fascia iliaca. (Note the reflection of the fascia close to the vertebral column.)

1. Quadratus lumbarum muscle
2. Psoas muscle
3. Iliacus muscle
4. Lateral cutaneous nerve of the thigh
5. Inguinal ligament
6. Femoral nerve
7. Sartorius muscle
8. Obturator nerve
9. Genitofemoral nerve
10. Medial attachment of the fascia iliaca to the vertebral column and upper part of the sacrum

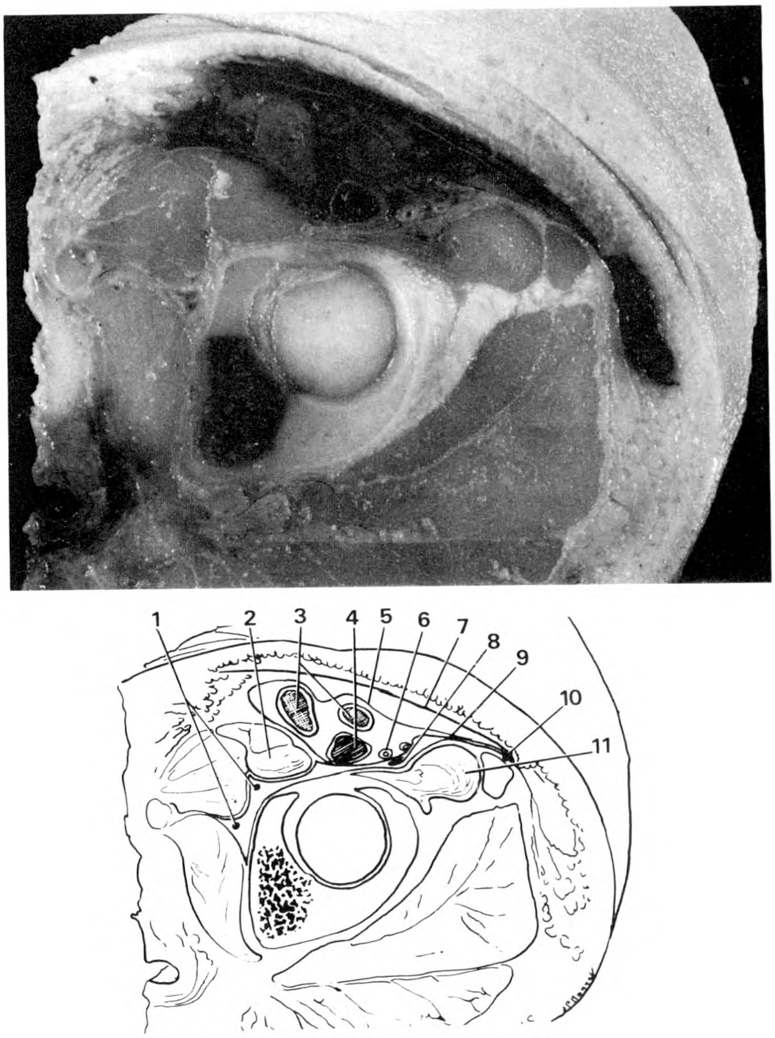


Figure 3. Transverse section at the root of thigh.

1. Division branches of the obturator nerve
2. Pectineal muscle
3. Femoral vein
4. Femoral artery
5. Fascia lata
6. Lacuna vasorum
7. Division branches of the lateral cutaneous nerve of the thigh
8. Femoral nerve
9. Psoas muscle
10. Lacuna musculorum

Table 1. Surgical Indications in Two Groups of Patients Anesthetized by 3-in-1 Block (Group 1) or Fascia Iliaca Compartment Block (Group 2)

Indication	Group 1	Group 2
Fracture of the femur	19	17
Surface operations of the thigh (wounds, skin grafts, abscesses)	11	9
Removal of implants and biopsies of the femur	15	10
Operations necessitating the placement of a tourniquet at the thigh	11	21
Slipped capital femoral epiphysis	4	3

calculated on weight basis in both groups: 0.7 mL/kg for children weighing less than 20 kg, 15 mL for those weighing 20 to 30 kg, 20 mL for 30 to 40 kg children, 25 mL for those 40 to 50 kg in weight, and 27.5 mL for those weighing over 50 kg.

Blocking procedures. A modification of the 3-in-1 block (1) using electrical stimulation for precise nerve location was used in group 1. With the patients in the supine position, the site of puncture was marked on the skin 0.5 to 1 cm below the inguinal ligament and lateral to the femoral artery. The block needle was advanced in a sagittal plane at a 30° angle to skin, pointing rostrally, until muscle twitches were elicited in the quadriceps femoris muscle. Then finger pressure was applied "gently but firmly just distal to the needle" (1) before injection, to force the anesthetic upwards. After the needle had been withdrawn, the finger pressure was maintained for a few minutes while the area was massaged to favor upward diffusion.

The technique of the fascia iliaca compartment block used the same dorsal recumbent position for the patients. A projection of the inguinal ligament was drawn on the skin from the pubic tubercle to the anterior superior iliac spine and divided in three equal parts. The site of puncture was marked 0.5 cm caudal to the point where the lateral joined the two

Table 2. Distribution of Anesthesia

	Femoral nerve		Lateral cutaneous nerve		Obturator nerve		Genitofemoral nerve[a]	
Anesthesia	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Complete								
Sensory	60	60	9	55[b]	8	53[b]	10	55
Motor	8	1	[c]	[c]	[d]	[d]	[a]	[a]
Incomplete								
Sensory	0	0	3	4	1	5	1	2
Motor	39	22[b]	[c]	[c]	[d]	[d]	[a]	[a]
Absent								
Sensory	0	0	48	1[b]	51	2[b]	49	3
Motor	13	37[b]	[c]	[c]	[d]	[d]	[a]	[a]

[a] Femoral branch of the genitofemoral nerve providing sensory supply to Scarpa's triangle.
[b] Significant difference when compared to group 1.
[c] The lateral cutaneous nerve of the thigh is a sensory nerve.
[d] The clinical test used for testing motor blockade did not allow definitive conclusions regarding the obturator nerve.

medial thirds of this line. The needle was inserted at a right angle to the skin while gentle pressure was exerted on the barrel of a syringe filled with the local anesthetic and connected to the block needle. A first "give" followed by a loss of resistance was felt as the tip crossed the fascia lata. The needle was advanced further until another "give" and another loss of resistance was felt as the fascia iliaca was pierced: the anesthetic solution was then injected, at the same time exerting a firm compression immediately caudal to the needle to favor the upward spread of the anesthetic. After the needle had been withdrawn, the swelling in the groin was firmly massaged to improve rostral diffusion of the local anesthetic within the fascia iliaca compartment.

Monitoring procedures and evaluation of anesthesia. Electrocardiogram tracings, respiratory rate, and blood pressure (Dinamap) were monitored during all procedures. Tidal volume, end-tidal CO_2, and halothane concentration were continuously monitored in patients given general anesthesia.

The blocking procedure was considered successful when the lateral, ventral, and medial aspects of the thigh were anesthetized permitting the scheduled surgical procedure to be completed on a motionless patient without any additional treatment. The extent of analgesia was evaluated in both groups at the end of the surgical procedure by skin pinching. Anesthesia was considered complete when no reaction or complaints of pain occurred during application of the nociceptive stimulus. It was considered incomplete if the patient either complained a little of pain or had motor responses not observed after pinching of adjacent areas.

Motor blockade was evaluated at the end of the operation in both groups, either by asking the patient to move his or her leg and/or by applying nociceptive stimuli aimed at eliciting withdrawal movements. (This crude evaluation was suitable for testing the quadriceps femoris muscle, supplied by the femoral nerve, but it did not permit conclusions regarding the function of the adductors of the thigh, supplied by the obturator nerve.)

The duration of the sensory block was measured as the time between injection and the first evidence of pain (complaints of pain; crying; grimacing; restlessness; or autonomic responses such as tachycardia, hypertension, or sweating) occurring either spontaneously or with hourly assessments using skin pinching of the ventral aspect of the thigh (supplied by the femoral nerve).

Statistical methods. Data from the two groups were compared using both parametric (Student's *t*-test) and nonparametric (Mann–Whitney test) tests. Qualitative parameters were evaluated using chi-square test. Differences were considered statistically significant at level $P < 0.05$.

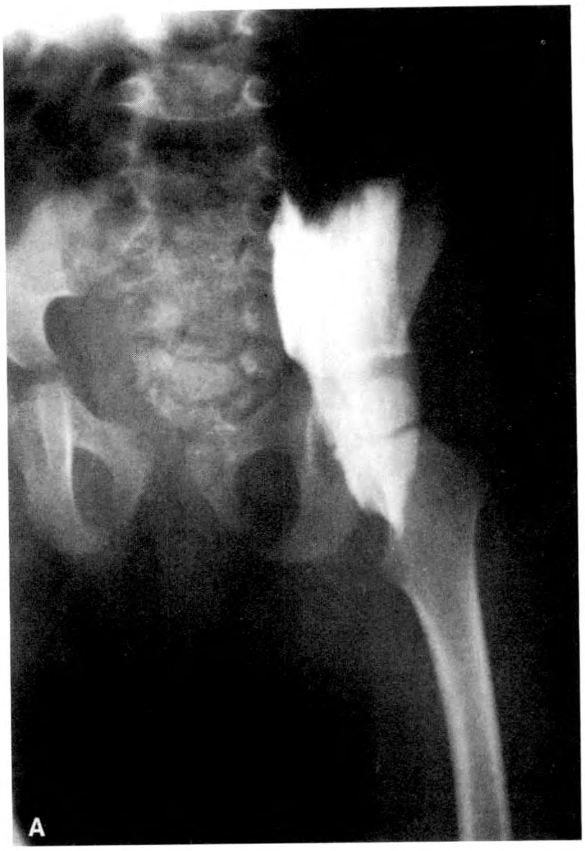
Results

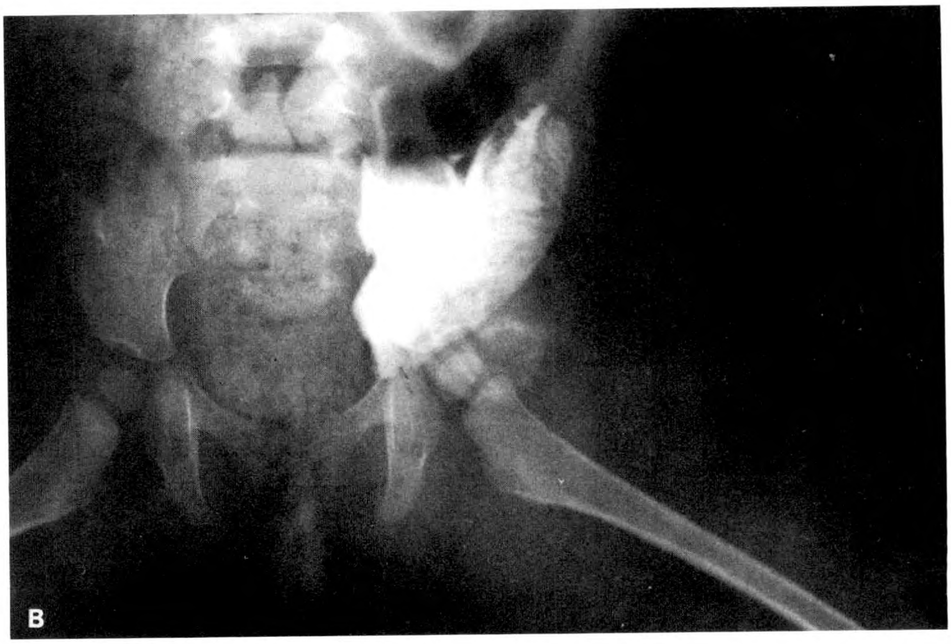
Patients in the two groups did not differ significantly with regard to age, weight, surgical indications, or gender. The same 2:1 predominance of males was seen in both groups.

Group 1 (3-in-1 Block)

The femoral nerve was located in every case on the first attempt in 51 procedures. In nine patients, a second attempt had to be made due to reflux of blood into the syringe (arterial in three, venous in two)

Figure 4. Spread of a solution containing contrast media (data from patients not included in the study protocol). (**A**) 3-in-1 block. Note that the solution does not reach the psoas compartment where the lumbar plexus lies. (**B**) Fascia iliaca compartment block. Note the spread of the solution along the anterior aspect of the iliacus muscle and the medial increase in opacity, probably due to superimposition resulting from the reflection of the fascia iliaca compartment covering successively: 1) the anterior aspect of the iliacus muscle, then 2) the posterior, and 3) the anterior aspects of the psoas muscle.





upon initial insertion of the needle or misplacement of the needle (absence of muscle twitches in four). During injection, swelling in the groin occurred in 11 patients. All patients developed a femoral block, but the procedure was totally successful only in 12 children, including the 11 individuals who developed swelling in the groin. The spread of the anesthetic solution when no swelling had occurred is shown in Figure 4A. The distribution of sensory and motor blockades is shown in Table 2. There were no complications, and postoperative pain relief lasted 6.2 ± 1.4 hours.

Group 2 (Fascia Iliaca Compartment Block)

The two characteristic "gives" resulting from the crossing of the needle through the fascia lata and then through the fascia iliaca were felt on the first attempt in 59 patients, and on the second attempt in one child. Swelling in the groin occurred in 59 patients, and the block procedure was successful in 55. The spread of the local anesthetic is shown in Figure 4B. The one patient who did not show any swelling in the groin developed a femoral nerve block only. The distribution of anesthesia is shown in Table 2: motor blockade of the femoral nerve developed less often in group 2 than in group 1 (a statistically significant difference [$P < 0.05$]), whereas sensory blockade of the lateral cutaneous, obturator, and the femoral branch of the genitofemoral nerves occurred more often (also statistically significant [$P < 0.05$]). No complications were observed and postoperative pain relief lasted 5.0 ± 1.3 h (significantly less than in group 1 [$P < 0.05$]).

Discussion

The fascia iliaca compartment block proved to be easy and free of adverse effects. The technique resulted in blocking the three main lumbar plexus nerves supplying the thigh in more than 90% of procedures and did not require expensive materials or unusual skills. On the other hand, the use of a nerve stimulator did not improve, and even worsened, the results of the 3-in-1 block procedure (1). These poor results were not due to misplacement of the needle since a femoral block developed in all patients, as confirmed by the spread of the local anesthetic within the perifemoral nerve sheath (Figure 4A). While suspecting the importance of the fascia iliaca, Winnie et al. (1) suggested that the local anesthetic injected within the femoral nerve sheath could spread upward, thus reaching the lumbar plexus, within the psoas compartment, and then spreading backward along the lateral cutaneous and obturator nerves. In their paper, the authors included radiographs taken after the injection of contrast material, but as seen in Figure 4A, the local anesthetic does not extend out of the pelvis and does not reach the psoas compartment. Furthermore, in our experience of lumbar plexus blocks (7), we did not observe any spread of anesthetic solution from within the psoas compartment, where the solution was directly introduced, towards either the femoral, lateral cutaneous, or obturator nerve. Thus, the hypothesis of Winnie et al. (1) is not supported even by their own data, and another explanation has to be found to explain why, in a number of patients, three separate nerves can be blocked by a single injection of a local anesthetic. In our group 1, 11 of the 12 patients with a block of the lateral cutaneous nerve developed swelling in the groin during injection. Our hypothesis is that these patients were, in fact, actually given a fascia iliaca compartment block and we think that at least in most cases, the 3-in-1 block is successful when the tip of the needle does not lie within the perifemoral nerve sheath, but outside of it (even if still very close to it), within the fascia iliaca compartment. Confirmation of this hypothesis can be found in the development of inadvertent 3-in-1 blocks following various peripheral nerve blocks at the thigh, such as lateral cutaneous nerve blocks (8,9). Since using a nerve stimulator improves the accuracy of the location of the femoral nerve, it may be expected that the tip of the block needle is inserted in and stays within the perifemoral nerve space (limited by the femoral nerve sheath) more often than after a blocking procedure eliciting paresthesias only. This may explain why the use of a nerve stimulator did not improve the distribution of anesthesia in group 2 but even worsened it.

Whereas the distribution of analgesia was significantly improved by using the fascia iliaca compartment block technique, the duration of postoperative pain relief was significantly reduced (by approximately 1 h). This may be due to the more extended spread of the local anesthetic to the vicinity of highly vascularized tissues (especially the iliacus muscle) as compared to the spread following a 3-in-1 block within the perifemoral nerve space, a space with a relatively poor venous drainage. Thus, the probably higher vascular uptake after fascia iliaca compartment blocks may account for the decrease in duration of postoperative analgesia.

In conclusion, the fascia iliaca compartment block technique is easy, reliable, and provides a high degree of sensory blockade of the lumbar plexus nerves that supply the thigh using reasonable amounts of local anesthetic. This technique requires neither unusual skills nor expensive devices, and it does not threaten any vital organ. We believe that this technique can be recommended for use in children.

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References

1. Winnie AP, Ramamurthy S, Durrani Z. The inguinal paravascular technic of lumbar plexus anesthesia: the "3-in-1" block. Anesth Analg 1973;52:989–96.
2. Chayen D, Nathan H, Chayen M. The psoas compartment block. Anesthesiology 1976;45:95–9.
3. Williams PL, Warwick R. Fasciae and muscles of the lower limb. In: Williams PL, Warwick R, eds. Gray's Anatomy, 36th ed. Philadelphia: WB Saunders, 1980:593–621.
4. Dalens B, Vanneuville G, Tanguy A. A new parascalene approach to the brachial plexus in children: comparison with the supraclavicular approach. Anesth Analg 1987;66:1264–71.
5. Dalens B, Hasnaoui A. Caudal anesthesia in pediatric surgery: success rate and adverse effects in 750 consecutive patients. Anesth Analg 1989;68:83–9.
6. Winnie AP. An "immobile" needle for nerve blocks. Anesthesiology 1969;31:577–8.
7. Dalens B, Tanguy A, Vanneuville G. Lumbar plexus block in children: a comparison of two procedures in 50 patients. Anesth Analg 1988;67:750–8.
8. Sharrock NE. Inadvertent "3-in-1 block" following injection of the lateral cutaneous nerve of the thigh. Anesth Analg 1980; 59:887–8.
9. Lonsdale M. 3-in-1 block: confirmation of Winnie's anatomical hypothesis. Anesth Analg 1988;67:601–2.

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1989;69:714–20

Hypertonic Saline Solution-Hetastarch for Fluid Resuscitation in Experimental Septic Shock

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ARMISTEAD CW JR, VINCENT J-L, PREISER J-C, DE BACKER D, LE MINH T. Hypertonic saline solution-hetastarch for fluid resuscitation in experimental septic shock. Anesth Analg 1989;69:714–20.

Hypertonic colloid solutions have been found efficacious in the resuscitation from hemorrhagic/traumatic shock. The present study investigated the hemodynamic, gasometric, and metabolic effects of hypertonic colloids in endotoxic shock in the dog. Thirty minutes after administration of 3 mg/kg normal body weight of Escherichia coli *endotoxin, dogs were randomly assigned to receive 10 mL/kg hydroxyethylstarch (HES) either in 0.9% NaCl (HES, 10 dogs) or in 7.5% NaCl (HT-HES, 10 dogs) in 30 min. Thereafter, 0.9% NaCl solution was administered in volumes adequate to maintain pulmonary artery balloon-occluded pressure at baseline levels. Total fluid administered averaged 64 ± 30 mL/kg (mean ± SD) in the HES group and 73 ± 34 mL/kg in the HT-HES group. As these differences were not statistically significant, total sodium load was higher in the HT-HES group. The persistent volume effect was associated with persistently lower hematocrit and protein levels in the HT-HES group. Initial fluid resuscitation with HT-HES resulted in arterial pressure, cardiac filling pressures, cardiac output, stroke volume, and rates of oxygen delivery and oxygen consumption that were greater than those with HES. Vascular resistances were similar. Analysis of left ventricular function curves also indicated an improvement in cardiac performance. However, these effects almost completely vanished during the remainder of the study. In the HT-HES group, serum sodium and osmolality levels increased to 167 ± 4 mEq/L and 344 ± 4 mOsm/kg H_2O, respectively. Therefore, in the initial fluid resuscitation from septic shock, hypertonic colloids can have beneficial effects that are attributed to an increase in plasma volume and an improvement in cardiac function; but these effects are only transient.*

Key Words: SHOCK, SEPTIC—resuscitation. FLUID BALANCE.

Hypertonic saline solutions have been effectively used for many years in the fluid resuscitation of animals (experimentally) and of patients with severe hypovolemia (1–6). Possible mechanisms responsible for the beneficial effects seen with these solutions include increased plasma volume (7,8), improved myocardial contractility (9,10), widespread vasodilation (11,12), and an as yet ill-defined reflex mechanism causing a sustained hemodynamic improvement independent of significant volume expansion (13,14). In circulatory shock, these effects also could be related to the reversal of cellular abnormalities (15).

The role of hypertonic solutions in the treatment of septic shock is less well defined. Hypertonic solutions of glucose, insulin, and potassium (GIK) increase cardiac output and oxygen consumption in septic shock both experimentally (16,17) and clinically (18). However, these effects appear to be related to the hyperosmolarity rather than to the metabolic effects of the mixture (17). In a recent study from our laboratory (19), hypertonic saline solution was used in the treatment of experimental endotoxic shock and was found to restore oxygen transport and consumption rapidly (19). Another recent study of experimental endotoxic shock related the hemodynamic improvement to the total sodium load administered, whether it was given isotonically or hypertonically (20).

The combination of hypertonic saline solution with

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colloids has been suggested as enhancing the vascular effects of these fluids (6,21–23). In bled sheep, the combination of hypertonic saline solution with dextran has been found superior to a number of other solutions of equal tonicity in maintaining plasma volume, mean arterial pressure, and cardiac output (22). Kramer et al. (22) used hypertonic saline solution-dextran for small volume resuscitation of sheep with severe hemorrhagic shock and found cardiac output, oxygen consumption, and urine output to be significantly greater than those with resuscitation with the same volume of lactated Ringer's solution. These authors recently used the same solution in the resuscitation of severely injured patients and observed a more rapid hemodynamic stabilization associated with an improved survival (6).

To our knowledge, hypertonic colloid solutions have not been used in the resuscitation from septic shock. In the present study, we evaluated the hemodynamic, gasometric, and metabolic effects of 6% hydroxyethylstarch (HES) in 0.9% NaCl or in 7.5% NaCl used in the initial fluid resuscitation from septic shock. We used an endotoxin dog model in which fluid administration produces a low resistance type of shock (19,24,25).

Methods and Material

Twenty mongrel dogs (28 ± 7 kg) were randomly divided into two groups of 10 each, one group to receive HES in 0.9% NaCl (Plasmasteril, Fresenius AG) and one group to receive HES in 7.5% NaCl (after sterile addition of NaCl in the hospital pharmacy) for initial resuscitative fluid. After an overnight fast with water available, the dogs were anesthetized with intravenous pentobarbital 25 mg/kg. Anesthesia was maintained with additional intravenous doses of 15–30 mg as needed. Cuffed endotracheal tubes were inserted and the lungs ventilated with a volume-cycled ventilator (Siemens-Elema 900 Servo) at a rate of 12 breaths/min and an FI_{O_2} of 0.21. Tidal volume was adjusted to maintain Pa_{CO_2} between 35 and 45 mm Hg. End-tidal CO_2 was monitored continuously (Capnograph 47210 A, Hewlett-Packard). Arterial and venous catheters (16G8, Becton, Dickinson and Co.) were placed surgically in the right femoral vessels and advanced to the distal aorta and inferior vena cava, respectively. A balloon-tipped flotation catheter (Swan-Ganz catheter model 93A-131H-7F, American Edwards Laboratories) was placed surgically in the right external jugular vein and advanced to the pulmonary artery. Position was confirmed by intravascular pressure waveforms. Heart rate and intravascular pressures were recorded (7404A recorder, Hewlett-Packard) on standard paper tracings. Cardiac output was measured by thermodilution technique with use of 5 mL of cold (<2°C) 5% dextrose in water at end-expiration. Three to six measurements were averaged. Blood gas tensions were measured by an automated analyzer (ABL2, Radiometer). Arterial and venous hemoglobin saturations were calculated and corrected for temperature and pH with use of Rossing and Cain's nomogram (26). The following baseline data were obtained before endotoxin administration: arterial pressure (AP), pulmonary artery pressure (PAP), pulmonary artery balloon-occluded pressure (PAOP), and right atrial pressure (RAP), cardiac output (CO), arterial and mixed venous blood gas tensions, hemoglobin and hematocrit, plasma protein and serum electrolyte levels, serum osmolarity, and arterial lactate concentration. After this, *E. coli* endotoxin (lipopolysaccharide *W. E. coli* 055:B5, Difco) 3 mg/kg was slowly injected (over 1 min) IV. Zero time (T_0) was taken as the start of this injection. The dogs were undisturbed for 30 min, after which all baseline measurements were repeated (T_{30}). The dogs were then given the appropriate initial resuscitative fluid according to prior randomization at 20 $mL \cdot kg^{-1} \cdot hr^{-1}$ for 30 min. At the end of this infusion (T_{60}), all baseline measurements were again repeated. Resuscitation was continued in both groups with 0.9% NaCl with the rate of infusion adjusted every 10 min to maintain PAOP at baseline (preendotoxin) levels. Intravascular pressures, cardiac output, arterial and mixed venous blood gas tensions were measured every hour. All baseline measurements were repeated at 240 min before the 0.9% NaCl infusion and mechanical ventilation were discontinued. Intravenous catheters were removed, wounds closed, and the dogs returned to their cages with tracheal tube still in place. The dogs were observed the morning after to determine mortality.

Stroke volume (SV), systemic (SVR) and pulmonary (PVR) vascular resistance, left (LVSW) and right (RVSW) ventricular stroke work, oxygen delivery (O_2del) and consumption ($\dot{V}O_2$), alveolar-arterial oxygen gradient (A-aO_2), and venous admixture ($\dot{Q}s/\dot{Q}t$) were calculated by the following formulas:

$$\text{SV (mL)} = \text{CO/HR},$$

$$\text{SVR (dynes}\cdot\text{sec}\cdot\text{cm}^{-5}) = (\text{AP} - \text{RAP}) \times 80/\text{CO},$$

$$\text{PVR (dynes}\cdot\text{sec}\cdot\text{cm}^{-5}) = (\text{PAP} - \text{PAOP}) \times 80/\text{CO},$$

$$\text{LVSW (g/m)} = \text{SV} \times (\text{MAP} - \text{PAOP}) \times 0.0136,$$

Table 1. Fluid and Sodium Intake in the Two Groups of Dogs

	Time intervals (min)			
	T_{30}–T_{60}	T_{60}–T_{120}	T_{120}–T_{180}	T_{180}–T_{240}
Fluid intake (mL/kg)				
HES	10.0	24 ± 12	20 ± 12	10 ± 10
HT-HES	10.0	21 ± 12	22 ± 12	20 ± 17
Sodium intake (mEq/kg)				
HES	1.5	3.8 ± 1.9	3.2 ± 2.1	1.7 ± 1.8
HT-HES	12.0	3.3 ± 1.9	3.4 ± 2.0	3.1 ± 2.8

$$\text{RVSW (g/m)} = \text{SV} \times (\text{PAP} - \text{RAP}) \times 0.0136,$$

$$\text{O}_2\text{del (mL/min)} = (\text{CO} \times \text{CaO}_2) \times 10,$$

$$\dot{\text{V}}\text{O}_2 \text{ (mL/min)} = \text{CO} \times (\text{CaO}_2 - \text{C}\bar{\text{v}}\text{O}_2) \times 10,$$

$$\text{A-aO}_2 \text{ (mm Hg)} = (\text{PBar} - 47) \times 0.21 - \text{PO}_2 + \text{PCO}_2/0.8,$$

$$\dot{\text{Q}}\text{s}/\dot{\text{Q}}\text{t (\%)} = (\text{CcO}_2 - \text{CaO}_2)/(\text{CcO}_2 - \text{C}\bar{\text{v}}\text{O}_2),$$

where CcO_2, CaO_2, and $C\bar{v}O_2$ represent the oxygen contents of pulmonary capillary and arterial and mixed venous blood, respectively. Cardiac output, SV, LVSW, RVSW, O_2del, and $\dot{V}O_2$ were referred to the weight of each dog.

Statistical evaluation was performed by a multivariate analysis of variance (MANOVA, SPSS update 9.0) for repeated measures designs, to evaluate the effects of time and treatment. Differences in fluids infused were evaluated by a Student's *t*-test for unpaired data. Differences in survival were evaluated by a χ^2 analysis. A 95% confidence level was accepted for statistical signification. Results are expressed as mean ± SD.

Results

Total fluid administered was 64 ± 30 mL/kg in HES and 73 ± 34 mL/kg in HT-HES (differences not significant). As there were no significant differences in sodium administered after initial resuscitation, total sodium load was higher in HT-HES (Table 1).

As anticipated, endotoxin administration was immediately followed by significant decreases in arterial pressure, filling pressures, and cardiac output (Figures 1 and 2). With initial fluid resuscitation, cardiac filling pressures increased more after HT-HES than after HES. Thereafter, they returned to baseline levels as part of the protocol (Figure 1). In the HT-HES group, arterial pressure also increased transiently; although this increase did not reach statistical significance (Figure 1). Pulmonary artery pressure followed a similar pattern. In the HT-HES group, heart rate was slightly higher after initial fluid resuscitation (Figure 2). Cardiac output was higher in the HT-HES group with the differences being significant at 60 and 120 min (Figure 2); it was also significantly above baseline at these times. Stroke volume followed a comparable course with differences being significantly greater also at the end of the study (Figure 2). During fluid infusion, systemic vascular resistance decreased significantly in both groups and remained decreased (Figure 3). There were no significant differences in systemic or pulmonary vascular resistance between the two groups.

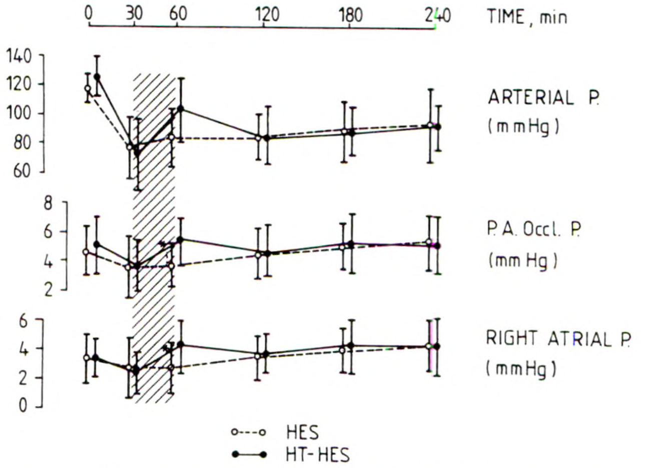

Figure 1. Changes in arterial pressure, pulmonary artery balloon-occluded pressure, and right atrial pressure over time in the dogs initially resuscitated (period represented by the shaded area) with normotonic HES (open circles, broken lines) or hypertonic HES (closed circles, continuous lines). Thereafter, all dogs were treated with normotonic saline solution. $^*P < 0.05$ between the two groups of animals.

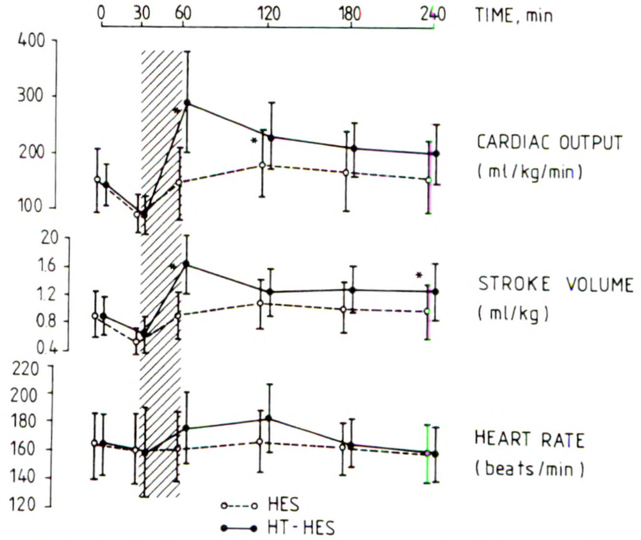

Figure 2. Evolution of cardiac output, stroke volume, and heart rate in the two groups of animals (see Figure 1).

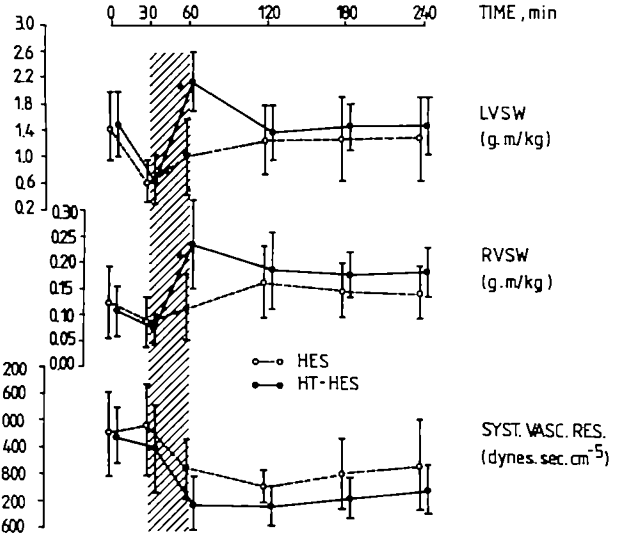

Figure 3. Changes in left ventricular stroke work, right ventricular stroke work, and systemic vascular resistance over time in the two groups of animals (see Figure 1).

At the end of the initial fluid resuscitation, both left ventricular and right ventricular stroke works were substantially higher after HT-HES (Figure 3). This suggested that cardiac performance improved, as pulmonary-artery balloon-occluded pressure, reflecting left ventricular end-diastolic pressure, reached values similar to those observed later during the study. This improvement in cardiac function, however, appeared transient (Figure 4).

After initial fluid resuscitation, the rate of oxygen delivery was higher in the HT-HES group and was associated with a greater oxygen consumption (Figure 5). Each dog had significant increases in blood lactate levels after endotoxin followed by some decrease with fluid resuscitation, but there were no significant differences between the two groups of animals (Table 2). Both groups had significant and similar increase in A-aO_2 and Qs/Qt during the study (Table 2 and Figure 5).

Hematocrit increased significantly in all dogs after endotoxin administration; it remained elevated in the HES group and decreased significantly in the HT-HES group (Table 2). Total serum protein levels decreased in both groups during the study but the decrease was greater in the HT-HES group. After HT-HES, serum sodium levels increased to 167 ± 4 mEq/L (range 159–172 mEq/L) and serum osmolarity to 344 ± 4 mOsm/kg H_2O (range 337–349 mOsm/kg H_2O). In the HES group, neither serum sodium nor osmolarity levels changed significantly. In the HT-HES group, serum potassium concentration decreased significantly but transiently to 2.8 ± 0.6 mEq/L (Table 2).

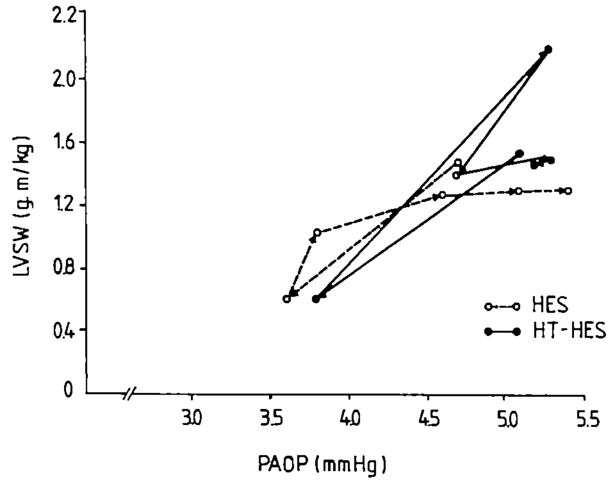

Figure 4. Left ventricular function curves represented by left ventricular stroke work versus pulmonary artery balloon-occluded pressure in the dogs treated with normotonic HES (open circles, broken lines) and with hypertonic HES (closed circles, continuous lines). The time intervals are the same as those in preceding figures. During initial fluid resuscitation (from the second to the third points), left ventricular function increased significantly more in the hypertonic group.

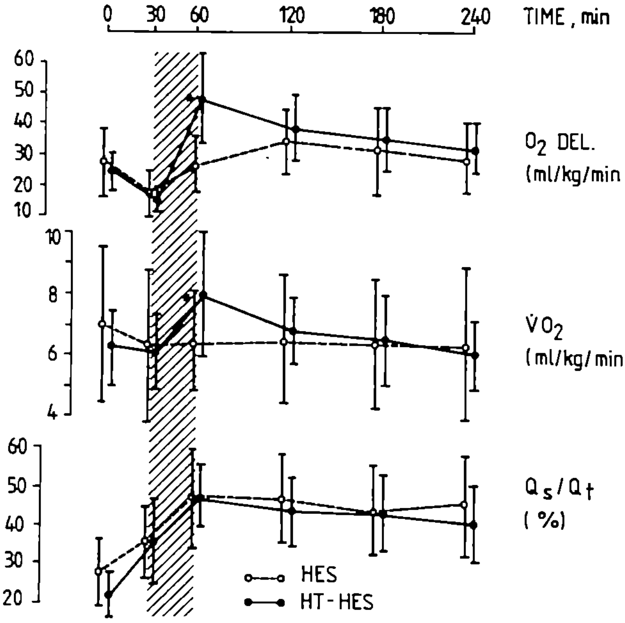

Figure 5. Evolution of O_2 delivery, O_2 consumption, and venous admixture in the two groups of animals (see Figure 1).

Three dogs in the HT-HES group and one dog in the HES group survived to the next morning. This difference in survival was not statistically significant.

Discussion

Hypertonic saline solutions can rapidly restore intravascular volume by pulling water from the intracel-

Table 2. Biochemical Changes Observed during the Study

	T_0	T_{30}	T_{60}	T_{240}
Hematocrit (%)				
HES	44 ± 7	51 ± 8[a]	52 ± 9[a]	48 ± 8[a]
HT-HES	40 ± 5	48 ± 8[a]	44 ± 7[b]	42 ± 10
Proteins (g/dL)				
HES	6.1 ± 0.7	5.9 ± 0.8[a]	4.6 ± 0.7[a]	3.9 ± 0.8[a]
HT-HES	5.8 ± 0.5	5.7 ± 0.7	3.9 ± 0.5[a,b]	3.5 ± 0.6[a]
Osmolarity (mOsm/kg H_2O)				
HES	307 ± 10	307 ± 9	309 ± 9	306 ± 7
HT-HES	297 ± 4	299 ± 5	344 ± 4[a,b]	326 ± 4[a,b]
Sodium (mEq/L)				
HES	150 ± 5	148 ± 5	147 ± 5	150 ± 5
HT-HES	145 ± 3	145 ± 2	167 ± 4[a,b]	161 ± 2[a,b]
Potassium (mEq/L)				
HES	3.5 ± 0.5	3.6 ± 0.5	3.3 ± 0.5	4.0 ± 0.6
HT-HES	3.5 ± 0.6	3.3 ± 0.6	2.8 ± 0.6[b]	4.0 ± 1.0
Lactate (mEq/L)				
HES	1.3 ± 0.5	4.3 ± 1.6[a]	3.9 ± 1.6[a]	3.1 ± 1.5[a]
HT-HES	2.4 ± 1.6	4.7 ± 2.2[a]	4.4 ± 2.0[a]	3.1 ± 1.6
A-aDO_2 (mm Hg)				
HES	24 ± 9	33 ± 12[a]	27 ± 10	26 ± 13
HT-HES	20 ± 13	32 ± 13	17 ± 13	28 ± 12

[a] $P < 0.05$ from baseline (T_0); [b] $P < 0.05$ between HES and HT-HES.

lular space into the interstitial and intravascular spaces (7). Hypertonic saline solutions may also improve myocardial performance by a direct effect on contractility (8–10) or by widespread precapillary vasodilation (11,12). Some hemodynamic effects can also result from a vagally mediated reflex mechanism triggered by the passage of hypertonic fluid through the pulmonary vascular bed (13,14). During shock states, improved myocardial performance can also be due to decreases in myocardial cell edema and restoration of myocardial cell transmembrane potentials (15,17).

In hemorrhagic shock, the combination of hypertonic saline solution with colloids provides both experimentally (22,23) and clinically (6) a greater and more sustained hemodynamic improvement than normotonic solutions. The proposed explanation is that the addition of colloids increases the plasma volume expansion. As fluid repletion remains a cornerstone in the management of septic shock and as colloids are often used in the early resuscitation of shock states, we compared the use of a given amount of colloids prepared either in normotonic or in hypertonic saline solution. We selected 6% hetastarch as the colloid component because it is both effective and safe even with relatively large volumes (27–29) and offers substantial cost advantages over albumin. We used 7.5% NaCl as the hypertonic saline solution component because this concentration appears to induce the maximal hemodynamic effects with overt toxicity (30). For this initial fluid resuscitation, we infused a standard amount of 10 mL/kg of colloid fluids, as this corresponds to the initial fluid requirements in this dog model (19,24,25).

The total amount of fluids required was not reduced in the dogs initially given HT-HES. This is surprising in view of the expected volume effect of the saline solution load, which was also associated with a significant increase in cardiac filling pressures. This also contrasts with previous studies in animals (20) and in humans (2–4,21) in which hypertonic solutions significantly decreased fluid requirements for resuscitation. This difference could be explained by an only transient volume effect of hypertonic solution in our model where fluid requirements were very high. However, the volume effect of HT-HES appeared maintained in view of the persistently lower proteins and hematocrit levels in this group. Hence, a larger blood volume was maintained in the presence of similar intravascular pressures, suggesting greater cardiovascular compliance, possibly related to a reduction of cellular edema with hyperosmolar solutions (7,17). It is also consistent with the vasodilating effect of those hypertonic solutions (11,12), although the lack of differences in vascular resistances plays down this phenomenon.

Cardiac output increased markedly after HT-HES to levels higher than those of baseline. The higher sodium load and the concurrent increase in cardiac filling pressures indicate that this was primarily due to a volume effect. The study of the left and the right ventricular function, however, also revealed a positive effect of the hypertonic solution on cardiac performance. An improvement in myocardial contractility could be related to a direct hyperosmolar effect (9,10), to a restoration of altered myocardial transmembrane potentials (15), or a decrease in myocardial edema (17). This latter mechanism, however, was unlikely as it occurred early and was only transient.

The higher cardiac output associated with hypertonic HES was accompanied by increases in oxygen transport and oxygen consumption, presumably reflecting a concurrent improvement in tissue blood flow (31,32). Thus, hypertonic solutions could shorten the cellular ischemia or hypoxia. Although plasma lactate levels tended to be lower in HT-HES, they were not significantly different in the two groups. Survival was also not significantly different between the two groups. Hence, the transient increase in oxygen delivery above baseline levels and the persistent volume effect of the hypertonic fluid were not shown to be beneficial.

Administration of hypertonic HES significantly increased serum sodium and osmolarity, which remained within relatively narrow ranges that would be clinically acceptable. Similar levels of serum sodium and osmolarity have been previously reported in human studies using hypertonic saline solution without adverse effects (3,4,33). Hypokalemia also occurred transiently and was probably due to an intracellular potassium shift, as it resolved spontaneously.

Hypertonic solutions can also have potentially beneficial effects in the presence of cerebral edema (34,35). They can also improve the distribution of pulmonary blood flow in the presence of acute lung injury (36,37). In the present study, hypertonic HES had no significant effect on blood gas tensions. Despite considerable venous admixture in this model, the formation of pulmonary edema is limited after endotoxin administration in the dog (38).

Our data indicate that hypertonic colloid solutions increase arterial pressure and cardiac output in the early resuscitation from septic shock. These effects appear related both to a volume effect and to an improvement in cardiac function. Hypertonic saline colloid solutions, therefore, offer a possible means for rapid restoration of hemodynamic stability in septic shock. However, the hemodynamic changes are largely transient, even though the effects on blood volume appear to persist. The long-term beneficial effects in the course of septic shock remain to be demonstrated.

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References

1. Velasco IT, Pontieri V, Rocha e Silva M, Lopes OU. Hyperosmotic NaCl and severe hemorrhagic shock. Am J Physiol 1980;239:H664–73.
2. Shackford SR, Norton CH, Todd MM. Renal, cerebral, and pulmonary effects of hypertonic resuscitation in a porcine model of hemorrhagic shock. Surgery 1988;104:553–60.
3. Monafo WW, Helverson JD, Schechtman K. The role of concentrated sodium solutions in the resuscitation of patients with severe burns. Surgery 1984;95:129–34.
4. Auler JOC, Pereira MHC, Gomide-Amaral RV, Stolf NG, Jatene AD, Rocha e Silva M. Hemodynamic effects of hypertonic sodium chloride during surgical treatment of aortic aneurysms. Surgery 1986;101:594–601.
5. Peters RM, Shackford SR, Hogan JS, Cologne JB. Comparison of isotonic and hypertonic fluids in resuscitation from hypovolemic shock. Surg Gynecol Obstet 1986;163:219–24.
6. Holcroft JW, Vassar MJ, Turner JE, Derlet RW, Kramer GC. 3% NaCl and 7.5% NaCl/Dextran 70 in the resuscitation of severely injured patients. Ann Surg 1987;206:279–87.
7. Wolf MB. Plasma volume dynamics after hypertonic fluid infusions in nephrectomized dogs. Am J Physiol 1971; 221:1392–5.
8. Mazzoni MC, Borgström P, Arfors KE, Intaglietta M. Dynamic fluid redistribution in hyperosmotic resuscitation of hypovolemic hemorrhage. Am J Physiol 1988;255:H629–37.
9. Koch-Weser J. Influence of osmolarity of perfusate on contractility of mammalian myocardium. Am J Physiol 1963; 204:957–62.
10. Rowe GG, McKenna DH, Corliss RJ, Sialer S. Hemodynamic effects of hypertonic sodium chloride. J Appl Physiol 1972; 32:182–4.
11. Lundvall J, Mellander S, White T. Hyperosmolarity and vasodilaton in human skeletal muscle. Acta Physiol Scand 1969; 77:224–33.
12. Gazitua SJ, Scott JB, Chou CC, Haddy FJ. Resistance responses to local changes in plasma osmolality in three vascular beds. Am J Physiol 1971;220:384–91.
13. Lopes OU, Pontieri V, Rocha e Silva M, Velasco IT. Hyperosmotic NaCl severe hemorrhagic shock: role of the innervated lung. Am J Physiol 1981;241:883–90.
14. Younes RN, Aun F, Tomida RM, Birolini D. The role of lung innervation in the hemodynamic response to hypertonic sodium chloride solutions in hemorrhagic shock. Surgery 1985; 98:900–6.
15. Nakayama SI, Kramer GC, Carlsen RC, Holcroft JW. Infusion of very hypertonic saline to bled rats: membrane potentials and fluid shifts. J Surg Res 1985;38:180–6.
16. Bronsveld W, Van Lambalgen AA, Van den Bos GC, et al. Ventricular function, hemodynamics and oxygen consumption during infusion of blood and glucose-insulin-potassium (GIK) in canine endotoxin shock. Circ Shock 1982;9:145–56.
17. Bronsveld W, van Lambalgen AA, Van Velzen D, van den Bos GC, Koopman PAR, Thijs LG. Myocardial metabolic and morphometric changes during canine endotoxic shock before and after glucose-insulin-potassium. Cardiovasc Res 1985; 19:455–64.
18. Bronsveld W, Van den Bos GC, Thijs LG. Use of glucose-insulin-potassium (GIK) in human septic shock. Crit Care Med 1985;13:566–70.
19. Luypaert P, Vincent JL, Domb M, et al. Fluid resuscitation with hypertonic saline in endotoxic shock. Circ Shock 1986; 20:311–20.
20. Mullins RJ, Hudgens RW. Hypertonic saline resuscitates dogs in endotoxic shock. J Surg Res 1987;43:37–44.

21. Smith GJ, Kramer GC, Perron P, Nakayama SI, Gunther RA, Holcroft JW. A comparison of several hypertonic solutions for resuscitation of bled sheep. J Surg Res 1985;39:517–28.
22. Kramer GC, Perron PR, Lindsey, et al. Small-volume resuscitation with hypertonic saline dextran solution. Surgery 1986; 100:239–46.
23. Carvajal HF, Parks DH. Optimal composition of burn resuscitation fluids. Crit Care Med 1988;16:695–700.
24. Vincent JL, Van der Linden P, Domb M, Blecic S, Azimi G, Bernard A. Dopamine compared with dobutamine in experimental septic shock: relevance to fluid administration. Anesth Analg 1987;66:565–71.
25. Vincent JL, Domb M, Van der Linden P, et al. Amrinone administration in endotoxic shock. Circ Shock 1988;25:75–83.
26. Rossing RG, Cain SM. A nomogram relating Po_2, pH, temperature and hemoglobin saturation in the dog. J Appl Physiol 1966;21:195–201.
27. Puri VK, Howard M, Paidipaty BB, Singh S. Resuscitation in hypovolemia and shock: a prospective study of hydroxyethylstarch and albumin. Crit Care Med 1983;11:518–22.
28. Shatney CH, Deepika K, Militello PR, Majerus TC, Dawson B. Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. Arch Surg 1983;118:804–9.
29. Rackow EC, Falk JL, Fein IA, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch and saline solutions in patients with hypovolemic and septic shock. Crit Care Med 1983;11:839–50.
30. Traverso LW, Bellamy RF, Hollenbach SJ, Witcher LD. Hypertonic sodium chloride solutions: effect on hemodynamics and survival after hemorrhage in swine. J Trauma 1987;27:32–9.
31. Shah DM, Powers SR Jr, Stratton HH, Newell JC. Effects of hypertonic mannitol on oxygen utilization in canine hind limbs following shock. J Surg Res 1981;30:593–601.
32. Maningas PA. Resuscitation with 7.5% NaCl in 6% dextran-70 during hemorrhagic shock in swine: effects on organ blood flow. Crit Care Med 1987;15:1121–6.
33. Shackford SR, Fortlage DA, Peters RM, Hollingsworth-Fridlund P, Sise MJ. Serum osmolar and electrolyte changes associated with large infusions of hypertonic sodium lactate for intravascular volume expansion of patients undergoing aortic reconstruction. Surg Gynecol Obstet 1987;164:127–36.
34. Todd MM, Concezione T, Moore S. Cerebral effects of isotonic hemodilution with a hypertonic saline solution. J Neurosurg 1985;63:944–8.
35. Gunnar W, Jonasson O, Merlotti G, Stone J, Barrett J. Head injury and hemorrhagic shock: studies of the blood brain barrier and intracranial pressure after resuscitation with normal saline solution, 3% saline solution, and dextran-40. Surgery 1987;103:398–407.
36. Powers SR, Shah D, Ryon D, et al. Hypertonic mannitol in the therapy of the acute respiratory distress syndrome. Ann Surg 1977;185:619–25.
37. Layon J, Duncan D, Gallagher TJ, Banner MJ. Hypertonic saline as a resuscitation solution in hemorrhagic shock: effects on extravascular lung water and cardiopulmonary function. Anesth Analg 1987;66:154–8.
38. Brigham KL, Meyrick B. Endotoxin and lung injury. Am Rev Respir Dis 1986;133:913–27.

Effects of Halothane on the Conduction System of the Heart in Humans

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SCHEFFER GJ, JONGES R, HOLLEY HS, GRIMBERGEN CA, ROS HH, PEPER A, BOOIJ LHDJ. Effects of halothane on the conduction system of the heart in humans. Anesth Analg 1989;69:721–6.

The effects of 2.0 MAC halothane on atrioventricular conduction times in humans were studied. A real-time recording system for the detection of surface His-Purkinje potentials based on signal averaging techniques was used. Recordings were made in 23 patients before and after the administration of halothane. In 18 patients we were able to measure atrial (P-H) and His-Purkinje (H-V) conduction times (78%). A small but statistically significant decrease in P-H conduction times from 115.3 ± 3.9 (SEM) to 110.8 ± 4.2 ms was found ($P \leq 0.01$). H-V conduction times did not change significantly. Heart rates decreased significantly from 87.6 ± 2.6 to 74.8 ± 2.5 beats/min ($P \leq 0.01$). Systolic blood pressures decreased from 118.9 ± 3.7 to 103.6 ± 4.2 mm Hg. It is concluded that the decrease in heart rate and the decrease in atrial conduction time caused by halothane can be explained by interactions of several different mechanisms. The specific combination of slowing heart rate and a decrease of atrial conduction time provides a possible explanation for atrial arrhythmias during the administration of halothane.

Key Words: ANESTHETICS, VOLATILE—halothane. HEART, CONDUCTION—atrioventricular.

Both in vivo and in vitro studies indicate that halothane impairs conduction in the specialized conducting system of the heart (1–3). Impaired conduction is a cause for heart block and for reentrant dysrhythmias (4). With invasive His bundle electrocardiography it is possible to localize the effects of anesthetics and other drugs on the atrial, atrioventricular (AV) nodal, or His-Purkinje portions of the conduction system in the canine heart (5–7). Catheter His bundle studies of the effects of anesthetics on atrioventricular conduction have not been performed in humans because of the considerable risk involved. Noninvasive recording of the electrical activity of the His-Purkinje system (HPS) was first reported in 1973 and proved to be a reliable and reproducible method (8–10). His-Purkinje signals obtained by this method have a smaller magnitude than interference signals from the body surface. In this study we used signal averaging techniques to increase the signal-to-noise ratio to recover the signals of the HPS (11). By using this method we were able to measure the atrial (P-H) and His-Purkinje (H-V) conduction times in humans during halothane administration in a noninvasive manner.

Patients and Methods

Twenty-three patients—aged 4–54 yr (mean, 22 yr), ASA physical status 1, unpremedicated, and undergoing a variety of minor elective surgical procedures—were studied. The study was approved by the local human ethics committee, and all patients or their parents gave written informed consent. All patients were studied before their scheduled surgical procedure started.

After the patients arrived in the operating room five self-adhesive silver-silver chloride electrocardiogram (ECG) electrodes (Hewlett-Packard 14389B) were applied to the chest, yielding two bipolar leads and one unipolar reference lead. The four electrodes were positioned in a square, with the sternal xiphoid as its center (Figure 1). The electrode spacing was 10 cm in adult patients and 3.5 cm in children (12). The recording system consisted of a battery-powered

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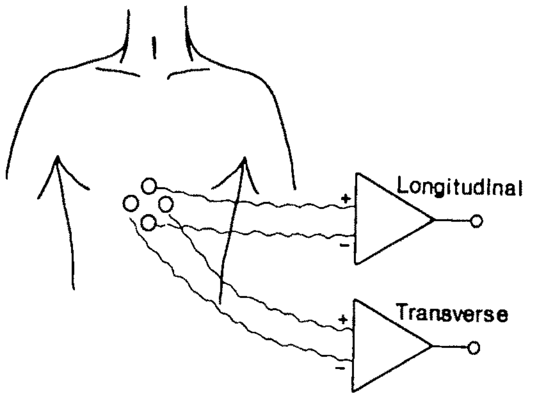

Figure 1. The two-dimensional surface field is recorded by a group of four electrodes, positioned in a square with the sternal xiphoid as center.

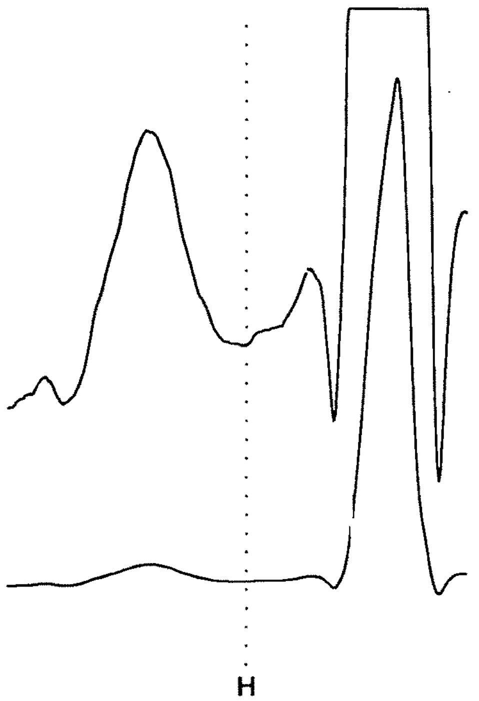

Figure 2. Example of a recording. The *lower trace* represents the normal ECG (lead II) for comparison. The *upper trace* represents the highly amplified averaged ECG recorded by the four electrodes (Figure 1). The optimal direction for the detection of the His bundle activity was determined. The number of sweeps was 298. The shape of the averaged signal differs significantly from that of the normal ECG because of different electrode localization and signal processing. This trace shows clearly the onset of the His-step.

four-channel preamplifier (gain = 1000), an analog-to-digital converter (Data Translation DT5716PGH), which converts the amplified signal with a sample frequency of 1000 Hz and a 16-bit resolution, and a signal processing system, based on an Intel 86/330 computer system.

The first HPS recording in each patient was made with the patient breathing oxygen for ~4 min. The patients were then anesthetized: they breathed halothane in oxygen spontaneously via facemask until the exhaled concentration of halothane corresponded with 2.0 MAC (Normac, Datex Inst. Corp.). If necessary, ventilation was assisted to maintain end-tidal Pco_2 at ~40 mm Hg. The second HPS recording was then made. Blood pressure was measured with a cuff around the arm using Korotkoff sound before and after the induction of anesthesia.

Conduction time intervals and heart rates were measured with the computer system. The system is able to perform A–D conversion, signal acquisition, triggering, and averaging in real time. The incoming signals and their cumulative average are displayed on a color monitor allowing for the immediate evaluation of the measurement. Recording time is ~3.5 min.

To improve the signal-to-noise ratio, signal averaging was applied. The basis of signal averaging is the assumption that the signal of interest has an unchanging time relation with a well-defined point in the signal—the reference or trigger point. Accurate triggering in the averaging procedure is essential for the preservation of the high-frequency content of the HPS signal (13). During the recordings the time interval between the HPS signal and trigger point before and after the administration of halothane must be sufficiently stable. The time interval between the HPS signal and the QRS complex fulfills this requirement. Because the moment of occurrence of the HPS signal and the beginning of the QRS complex has a fixed time relation, the QRS complex is used as the trigger point. The morphology of the surface His-Purkinje signal has been described in previous publications (12,14). Surface activity picked up from the AV node is very small, probably due to the multidirectional nature of the activity within the node (15). The transition to the unidirectional activity in the His bundle causes a steplike phenomenon in the surface signal (12,14) (Figure 2). This surface signal remains constant during the passage of the wavefront through the bundle of His. When the bundle branches are activated, both the direction and the magnitude of the activity changes, resulting in a change of amplitude of the surface signal. To be less dependent on directional changes of the activity of the heart the total two-dimensional surface field at the site of the measurement is registered (12,14).

The H-V interval is defined as the interval between the onset of the HPS activity and the first ventricular activity. As we recorded the total two-dimensional surface field, we were also able to determine the optimal direction for the detection of HPS activity. The shape of the signal thus found differs largely from that of the surface ECG (Figure 2). The P-H interval is defined as the beginning of the P wave and

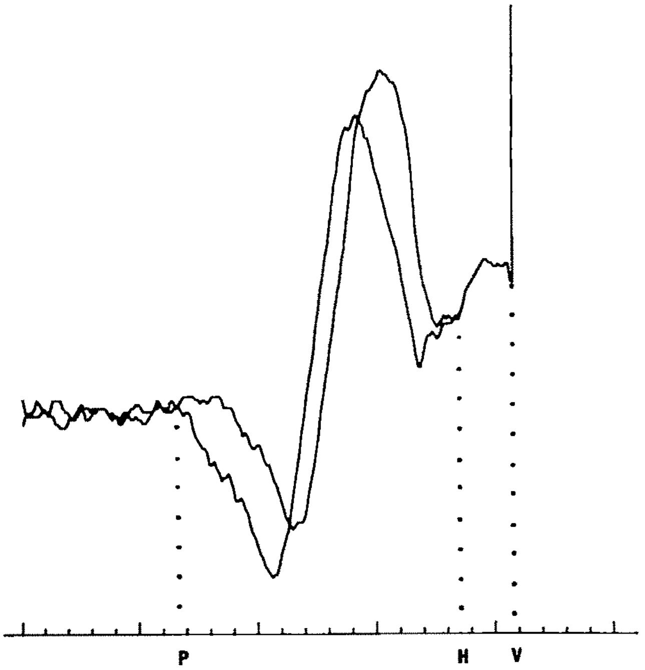

Figure 3. A conditional coherent averaged ECG, allowing a better estimation of the beginning of the P wave. *P* is the reference point of atrial activity, *H* is the reference point of His-Purkinje activity, and *V* is the reference point of ventricular activity. Each division represents 10 ms.

Table 1. Anesthetic Effects of Halothane on Atrial (P-H) and His-Purkinje (H-V) Conduction Times, and Changes in P-Wave Morphology (M) in Humans

	Intervals (ms)				
	Awake		Halothane (2.0 MAC)		
Patients	P-H	H-V	P-H	H-V	M
1	112	32	107	32	Yes
2	133	33	134	31	Yes
3	142	31	151	31	Yes
4	119	33	114	33	No
5	114	37	104	37	No
6	117	28	106	32	Yes
7	112	35	101	35	No
8	146	28	138	28	No
9	83	32	93	32	Yes
10	122	25	108	21	No
11	140	28	140	28	No
12	109	33	98	33	No
13	106	37	105	38	No
14	101	29	96	30	No
15	95	46	85	43	Yes
16	108	38	108	38	No
17	102	31	98	30	No
18	114	41	108	41	Yes

P-H interval awake averaged (SEM), 115.3 ± 3.9; P-H interval 2.0 MAC halothane (SEM), 110.8 ± 4.2; H-V interval awake averaged (SEM), 33.2 ± 1.2; and H-V interval 2.0 MAC halothane (SEM), 32.9 ± 1.2. P-wave morphology changed in seven patients after the administration of halothane.

the onset of the HPS signal. The frequency content of the first part of atrial depolarization is low, and it is sometimes difficult to estimate the correct beginning of the P wave. We used a special averaging technique for differentiation of the beginning of the P wave from interfering noise and the preceding T wave. This so-called conditional coherent averaging technique is based on the occurrence of physiologic AV node conduction time variations resulting in differences in the time intervals between the P wave and the QRS complex (13,16). The AV node conduction time variations can therefore be measured on a beat-by-beat basis by measuring the corresponding P-R intervals. The derived distribution of these intervals will be a Gaussian distribution with a mean P-R interval and a standard deviation. The next step is to divide the distribution into two subdistributions. Each subdistribution consists of a group of intervals longer than the mean interval and a group of intervals shorter than the mean interval. The subdistributions are averaged separately, resulting in two averaged complexes that show a difference in P-R interval. This technique allows for a better estimation of the beginning of the P wave (Figure 3).

All data are reported as mean ± SEM. The results before and after the administration of halothane were statistically evaluated using Student's *t*-test for paired data. A probability level of ≤0.05 was considered significant.

Results

In 18 of our 23 patients (78%) we were able to detect HPS activity and measure P-H and H-V intervals. In five patients we were not able to detect HPS activity because of excessive noise or P wave overlap. The P-H and H-V intervals are summarized in Table 1. There was a slight but significant decrease in the P-H conduction time from 115.8 ± 3.9 before to 110.8 ± 4.2 ms after administration of halothane ($P \leq 0.01$). In 13 of 18 patients the P-H interval decreased during halothane anesthesia (Figure 4). In two patients the P-H interval remained the same before and after administration of halothane, and in three patients the P-H interval increased. The H-V intervals did not change significantly from 33.2 ± 1.2 to 32.9 ± 1.2 ms. Heart rates decreased significantly from 87.6 ± 2.6 to 74.8 ± 2.5 beats/min ($P \leq 0.01$). Systolic blood pressures decreased from 118.9 ± 3.7 to 103.6 ± 4.2 mm Hg ($P \leq 0.01$). Diastolic blood pressures decreased from 75.8 ± 3.6 to 64.7 ± 3.1 mm Hg ($P \leq 0.01$). Data

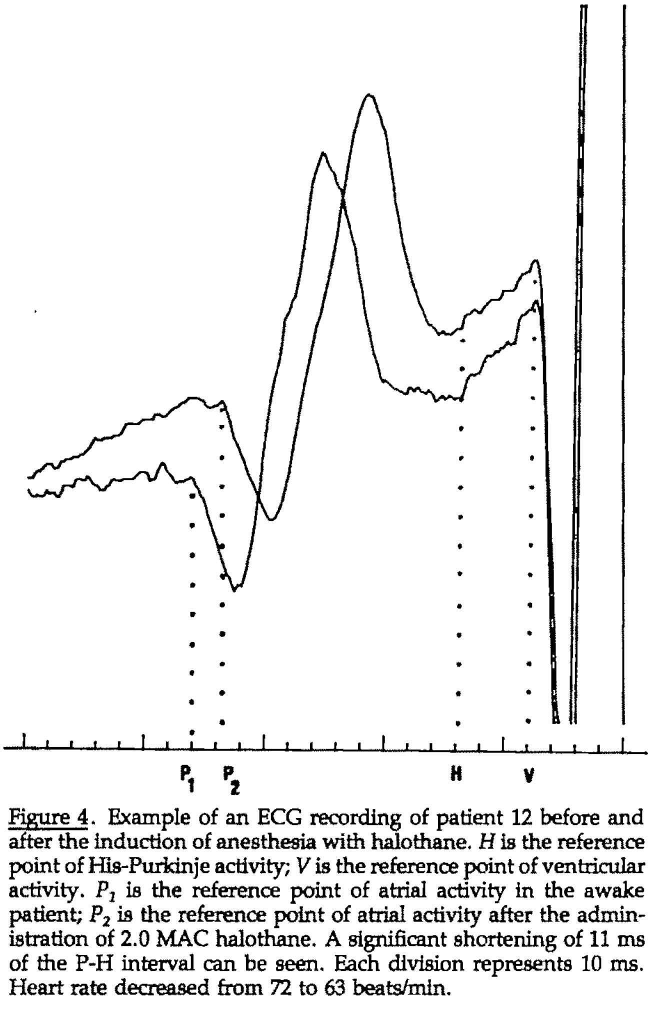

Figure 4. Example of an ECG recording of patient 12 before and after the induction of anesthesia with halothane. *H* is the reference point of His-Purkinje activity; *V* is the reference point of ventricular activity. P_1 is the reference point of atrial activity in the awake patient; P_2 is the reference point of atrial activity after the administration of 2.0 MAC halothane. A significant shortening of 11 ms of the P-H interval can be seen. Each division represents 10 ms. Heart rate decreased from 72 to 63 beats/min.

Table 2. Systolic (SBP) and Diastolic (DBP) Arterial Blood Pressures and Heart Rate (HR) Before and After Induction with 2.0 MAC Halothane[a]

	SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)
Awake	118.9 ± 3.7	75.8 ± 3.6	87.6 ± 2.6
Halothane	103.6 ± 4.2	64.7 ± 3.1	74.8 ± 2.5

[a] Values are mean ± SEM. $P \leq 0.01$.

are summarized in Table 2. In seven patients a marked difference in P-wave morphology before and after the administration of halothane occurred in the highly amplified signal, whereas in the other patients P-wave morphology did not change. On the normal ECG all patients had normal sinus rhythm, and no conversion to junctional rhythm was seen.

Discussion

Effects of halothane on the specialized conduction system have been studied extensively. Most of these experiments were carried out in animals or in single cardiac cells (1–3,6,7). To our knowledge there are no data on the effects of halothane on the conduction system of the heart in humans. Our data on the effects of halothane in the intact human, however, are difficult to interpret because of the many variables involved (e.g., reflexes, different intrinsic heart rates, autonomic control). The decrease in heart rate and the change in P-H conduction time in our patients may in part be explained by the loss of awareness and excitement after the induction of anesthesia and may not be an effect of halothane alone. On the other hand, studies using the human model can help to explain some of the clinical effects of halothane.

Our measurements in humans with noninvasive signal averaging techniques during the induction of anesthesia with 2.0 MAC halothane did not show a significant effect on His-Purkinje conduction time. This observation differs from those reported by others. Atlee et al. (7) observed a 2-ms increase in His-Purkinje conduction time during the induction of anesthesia with 1.2 MAC halothane in dogs. However, our data obtained in humans agree with those reported by Morrow et al. (17) and Hart et al. (18), who also found no change in H-V conduction time in dogs during halothane administration.

At first sight, the slight decrease in atrial conduction time in our study seems to contradict the prolongation of AV-node conduction time found during halothane anesthesia in animals by other investigators. Atlee and Rusy (6) have shown that halothane prolongs A-V conduction during rapid atrial pacing in dogs. In a later study Atlee et al. (7) found that halothane prolongs AV node conduction times in chronically instrumented dogs. They explained the depression of AV-node conduction as an indirect rather than a direct effect of halothane. The depressant effect of halothane on the AV node appeared to be mediated largely by removal of sympathetic tone. Only a small direct depressant effect of halothane on AV node conduction time was apparent in dogs automatically blocked with both atropine and propranolol. This suggests an indirect effect of halothane, because the effects of the autonomic nervous system on impulse formation and conduction are mainly concentrated on the supraventricular part of the conduction system (19).

Our study involved humans, and no invasive measurement methods or artificial cardiac pacing techniques were used. In invasive studies sutured epicardial electrodes are used, and the A-H interval is defined as the period from the beginning of atrial activity in the intraaortic electrogram and the beginning of the His potential, or as the time difference between the onset of the rapid deflection of the low atrial potential in the His bundle electrogram and the beginning of the His potential (18,20). We defined supraventricular conduction time as the difference between the beginning of the P wave and the onset of His-Purkinje activity in the amplified and averaged surface signal. The onset of the P wave in the surface electrogram originates from the first atrial excitation from any exit site of the sinus node and gives, consequently, a better approximation of the true onset of atrial activity. Ours is a different experimental arrangement compared with measurements made by electrodes sutured at a fixed place in the atrial epicardium. In seven of our 18 patients we noticed significant changes in P-wave morphology in the highly amplified signal. Boineau et al. (21) extensively studied the basis for changes in the configuration of the P wave in the surface ECG. They observed a relation between heart rate and P-wave morphology. Changes in P-wave morphology during sinus rhythm were referred to as intranodal pacemaker shifts leading to different atrial activation sequences. Increasing vagal stimulation led to lower foci of excitation near the AV node. It should be realized that the P-H interval is not only defined by conduction time in the AV node, but also by the intraatrial conduction time from the exit site of the sinus node to the entrance of the AV node. The decrease in heart rate in our study was presumably mediated by a relative increase in vagal tone due to halothane (7) and may have led to lower intranodal excitation as well (21). A resulting shortening of intraatrial conduction time may explain the slight decrease in total P-H conduction time. Our system is, alas, not yet able to give information about AV node conduction time. The fact that in two patients P-H intervals remained the same and in three patients the P-H intervals increased may be due to interindividual differences in autonomic tone during the induction of anesthesia.

The changes in supraventricular conduction during induction with halothane in our study with humans are difficult to explain. Possible mechanisms for the effects on heart rate and A-V conduction include both a direct effect of halothane and indirect effect due to a decrease in sympathetic tone. The mechanism by which adrenergic and cholinergic inputs regulate heart rate and conduction by their action on cardiac cells is complex and not yet explained. In addition, the observed phenomena in our study depend on additional variables, including differences in basal heart rate and autonomic tone. The decrease of atrial conduction time also may have been due to a baroreflex-mediated increase in sympathetic tone because of the reduction of blood pressure caused by halothane.

In summary, our findings demonstrate that the induction of anesthesia with 2.0 MAC halothane does not affect His-Purkinje conduction time in humans. Our study showed an unexpected decrease in P-H conduction time in combination with decreased heart rate. The different P-wave morphology that occurred in seven patients after induction with halothane indicates an intranodal shift of the dominant pacemaker localization. The results of our present study and those of other studies are not directly comparable because of differences in species and methods. We believe, however, that our findings in humans of an unchanged H-V conduction time and, in addition, a decreased P-H conduction time in combination with decreased heart rate may contribute to the knowledge of the effects of inhalation anesthetics in clinical anesthesia and merit further investigation.

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References

1. Reynolds AK, Chiz JF, Pasquet AF. Halothane and methoxyflurane: a comparison of their effects on cardiac pacemaker fibers. Anesthesiology 1972;36:112–8.
2. Atlee JL. Perioperative cardiac dysrhythmias. Chicago: Year Book Medical Publishers, 1985:151–62.
3. Turner LA, Bosnjak ZJ, Kampine JP. Actions of halothane on the electrical activity of Purkinje fibers derived from normal and infarcted canine hearts. Anesthesiology 1987;67:619–29.
4. Hofman BF, Rosen MR. Cellular mechanisms for cardiac arrhythmias. Circ Res 1981;49:1–15.
5. Scherlag BJ, Helfant RH, Damato AN. A catheterization technique for His bundle stimulation and recording in the intact dog. J Appl Physiol 1968;25:425–8.
6. Atlee JL, Rusy BF. Halothane depression of AV conduction studied by electrograms of the bundle of His in dogs. Anesthesiology 1972;36:112–8.
7. Atlee JL, Brownlee SW, Burstrom RE. Conscious-state comparisons of the effect of inhalation anesthetics on specialized atrioventricular conduction times in dogs. Anesthesiology 1986;64:703–10.
8. Berbari EJ, Lazzara R, Scherlag BJ. Surface recording technique for detecting electrical activity during the P-R segment. Am J Cardiol 1973;31:1–20.
9. Flowers NC, Horan LG. His bundle and bundle branch recording from the body surface. Circulation 1973;4(Suppl 4):102.
10. Feyter PJ, Ros HH, Majid PA, van Eenige MJ, Karreman J, Roos JP. Clinical evaluation of His-bundle electrogram recorded from the body surface. Clin Cardiol 1980;4:80–6.
11. Ros HH, Koeleman ASM, Van den Akker TJ. The technique of signal averaging and its practical application in the separation

of atrial and His-Purkinje activity. In: Hombach V, Hilger HH, eds. Signal averaging technique in clinical cardiology. Stuttgart: Schattauer Verlag, 1983:3–14.

12. Peper A, Jonges R, Losekoot TG, Grimbergen CA. Recording of surface His-Purkinje potentials. Med Biol Eng Comput 1985;23:365–76.
13. Rompelman O, Ros HH. Coherent averaging techniques: a tutorial review. Parts 1 and 2. J Biomed Eng 1985;8:24–35.
14. Peper A, Jonges R, Losekoot TG, Grimbergen CA. Separation of His-Purkinje potentials from coinciding atrium signals: removal of the P wave from the electrocardiogram. Med Biol Eng Comput 1982;20:195–201.
15. Janse MJ. Influence of the direction of the atrial wavefront on AV nodal transmission in isolated hearts of rabbits. Circ Res 1969;25:439.
16. Ros HH, Koeleman ASM, Van den Akker TJ. The dynamic behaviour of time intervals in the ECG. In: Kitney RI, Rompelman O, eds. The beat-by-beat investigation of cardiovascular function. Oxford: Clarendon Press, 1987:126–45.
17. Morrow DH, Logic JR, Haley JV. Antiarrhythmic anesthetic action: the effect of halothane on canine intracardiac impulse conduction during sinus rhythm. Anesth Analg 1977;56:187–93.
18. Hart AP, Royster RL, Johnston WE. Cardiac conduction of propranolol and verapamil with halothane in pentobarbitone-anesthetized dogs. Br J Anaesth 1988;61:748–53.
19. Moore EN, Spear JF. Effect of autonomic activity on pacemaker function and conduction. In: Wellens HJJ, Lie KI, Janse MJ, eds. The conduction system of the heart. Leiden: Stenfert Kroese, 1976:100–10.
20. Atlee JL, Dayer AM, Houge JC. Chronic recording from the His bundle of the awake dog. Basic Res Cardiol 1984;79:627–38.
21. Boineau JP, Schuessler RB, Mooney CR, et al. Multicentric origin of the atrial depolarization wave: the pacemaker complex. Circulation 1978;58:1036–48.

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1989;69:727–31

Effects of Parenteral Amino Acid Nutritional Regimens on Oxidative and Conjugative Drug Metabolism

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PANTUCK EJ, WEISSMAN C, PANTUCK CB, LEE YJ. Effects of parenteral amino acid nutritional regimens on oxidative and conjugative drug metabolism. Anesth Analg 1989;69:727–31.

Our goals were to determine the time-course of the increase in oxidative drug metabolism that occurs when parenteral nutrition is changed from dextrose to amino acids (23% branched-chain), whether the composition of the amino acid regimen influences this effect, and whether drug conjugation is similarly altered. We examined in healthy volunteers the effects of changing isocalorically from intravenous dextrose 440 kcal/day to amino acids, on one occasion 23% branched-chain and on another 85%. The change to the 23% regimen produced a significant increase in metabolic clearance of antipyrine, a model for oxidation (mean ± SE 3.0 ± 0.3 to 3.7 ± 0.4 L/h, N = 6, P < 0.003), but the change to the 85% regimen did not, indicating that the composition of an amino acid infusion can influence its effect on oxidative metabolism. Analysis of the concentration-time curve for antipyrine after simultaneous dosing and start of the 23% regimen suggests that the increase in metabolic capacity occurred within a few hours. Metabolic clearance of acetaminophen, a model for conjugation, was not altered by changing to either amino acid regimen.

Key Words: PROTEIN, AMINO ACID PARENTERAL NUTRITION. METABOLISM, NUTRITION—amino acids. BIOTRANSFORMATION (DRUG)—amino acid parenteral nutrition.

The composition of the diet can markedly affect oxidative drug metabolizing capacity in humans. Antipyrine, theophylline, propranolol, and estradiol are metabolized more rapidly by healthy adults when they eat a high-protein, low-carbohydrate diet than when they eat an isocaloric low-protein, high-carbohydrate diet (1–6). The same is true of theophylline in asthmatic children (7).

The use of total parenteral nutrition has become common in the management of seriously ill patients. Such individuals are likely to be receiving multiple drugs. A previous study from our laboratory showed that when healthy volunteers receiving a typical hospital semi-starvation regimen of 5% dextrose administered intravenously that provided 440 kcal/day were switched isocalorically to an intravenous infusion of amino acids for just 1 day, there was an increase in the rate at which they metabolized antipyrine (8). An increase in metabolism of the magnitude of the increase in antipyrine metabolism that occurred in some of these individuals would be expected to alter significantly the efficacy or toxicity of many therapeutic agents. A recent case report described a decrease from a therapeutically adequate, stable plasma concentration of theophylline to a concentration well below the lower end of the therapeutic range after an increase in the level of parenteral amino acid administration without any other change in therapy (9).

The mechanisms by which protein and carbohydrate affect oxidative drug metabolism in humans have not been established. It is possible that the effects of protein or intravenous amino acids on oxidative drug metabolism are due to particular amino acids. As a result of studies suggesting that parenteral nutritional solutions of amino acids with a high content of branched-chain amino acids (leucine, isoleucine, valine) are more effective than conventional amino acid solutions in restoring body cell mass in severely stressed patients (10,11), branched-chain enriched amino acid solutions have been re-

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cently introduced into clinical practice. Because branched-chain enriched amino acid solutions differ substantially from conventional solutions in their amino acid composition, they may also differ in their effects on oxidative drug metabolism.

Conjugation, like oxidation, is a major route of drug metabolism and plays an important role in the inactivation and elimination of many drugs. It is not known whether alterations in the protein or carbohydrate content of the human diet influence drug metabolism by conjugation.

The purpose of the present study was threefold: 1) to determine whether the effect on antipyrine metabolism of changing the composition of an intravenous infusion from dextrose to amino acids would be influenced by the branched-chain amino acid content of the amino acid regimen; 2) to determine the approximate time of onset, and, within the length of the study, the duration of progression of alterations in rate of elimination of antipyrine from plasma resulting from changing from dextrose to conventional or branched-chain enriched amino acid regimens; and 3) to determine whether these changes in intravenous caloric source alter conjugation of acetaminophen. We selected antipyrine and acetaminophen for study because they have been extensively used as model substrates to assess oxidative and conjugative drug metabolizing capacity, respectively (12–15).

Methods

Our subjects were eight healthy, male, young adult volunteers. No subject was a heavy drinker of alcohol, coffee, or tea or used any drug regularly. The study was approved by the Institutional Review Board of Columbia University and written informed consent was obtained from the subjects.

The subjects were admitted to the Surgical Metabolism Unit of the Columbia-Presbyterian Medical Center. They were permitted nothing by mouth except for water as desired, and an intravenous infusion of 5% dextrose in normal saline solution 440 kcal/day was begun. Twenty-four hours later, antipyrine 6 mg/kg body weight was administered orally with 200 mL of water. Samples of saliva for determination of antipyrine content were collected before the dose and every 30 min for the next 8 h, every hour for the next 16 h, and then every 2 h for the next 24 h. Salivary antipyrine concentrations correspond closely to serum concentrations (16). Nineteen hours after the dose of antipyrine, acetaminophen 1625 mg was administered orally with 200 mL of water. Blood samples for determination of plasma concentration of acetaminophen and its glucuronide and sulfate conjugates were obtained before and at 0.5, 1, 2, 3, 4, 5, 7, 9, 11, and 24 h after the dose. Urine for determination of acetaminophen metabolite content was collected for 24 h after the dose. Forty-eight hours after the dose of antipyrine, the intravenous infusion was changed isocalorically from dextrose to an amino acid solution and at the same time a second dose of antipyrine was given, followed 19 h later by a second dose of acetaminophen. Saliva, blood, and urine were collected as described previously. The subjects, except for two who did not return, were studied twice. On one occasion (order determined randomly), the amino acid solution was branched-chain enriched (85% content of branched-chain amino acids) and on the other was conventional (23% content of branched-chain amino acids). The interval between the two studies was at least 1 wk. The conventional amino acid solution was Aminosyn 3.5% (Abbott Laboratories, North Chicago, Ill.) and the branched-chain enriched solution was prepared by combining 4% Branchamin (Travenol Laboratories, Deerfield, Ill.) with Aminosyn 3.5%.

The saliva samples were analyzed for antipyrine content by the radioimmunoassay method of Chang et al. (17). Plasma concentrations of acetaminophen and its glucuronide and sulfate conjugates were determined with use of the high-pressure liquid chromatography method of Adriaenssens and Prescott (18). Urine was analyzed for content of the glucuronide, sulfate, cysteine, mercapturic acid, and 3-methoxysulfate conjugates of acetaminophen by a modification of the high-pressure liquid chromatography method of Howie et al. (19) described previously (20). Concentration of antipyrine-time data were fitted to a biexponential model with use of the nonlinear least-squares regression curve-fitting computer program NONLIN84 (Statistical Consultants, Inc., Lexington, Ky.) (21) and run analysis was performed to determine statistically whether the observed data points deviated systematically from the calculated best fit lines (22). Drug elimination rate constant (k) and half-life ($t_{1/2}$) were estimated from the terminal portion of the log concentration of drug-time curve by least-squares linear regression analysis. Area under the curve (AUC) was calculated by the linear trapezoidal method until the last measured concentration and then extrapolated to infinity by using the ratio to k of the value for this data point estimated from the calculated best fit line. Metabolic clearance rate (MCR) was calculated by dividing dose of drug by AUC. Apparent volume of distribution (aVd) was determined by dividing MCR by k. These

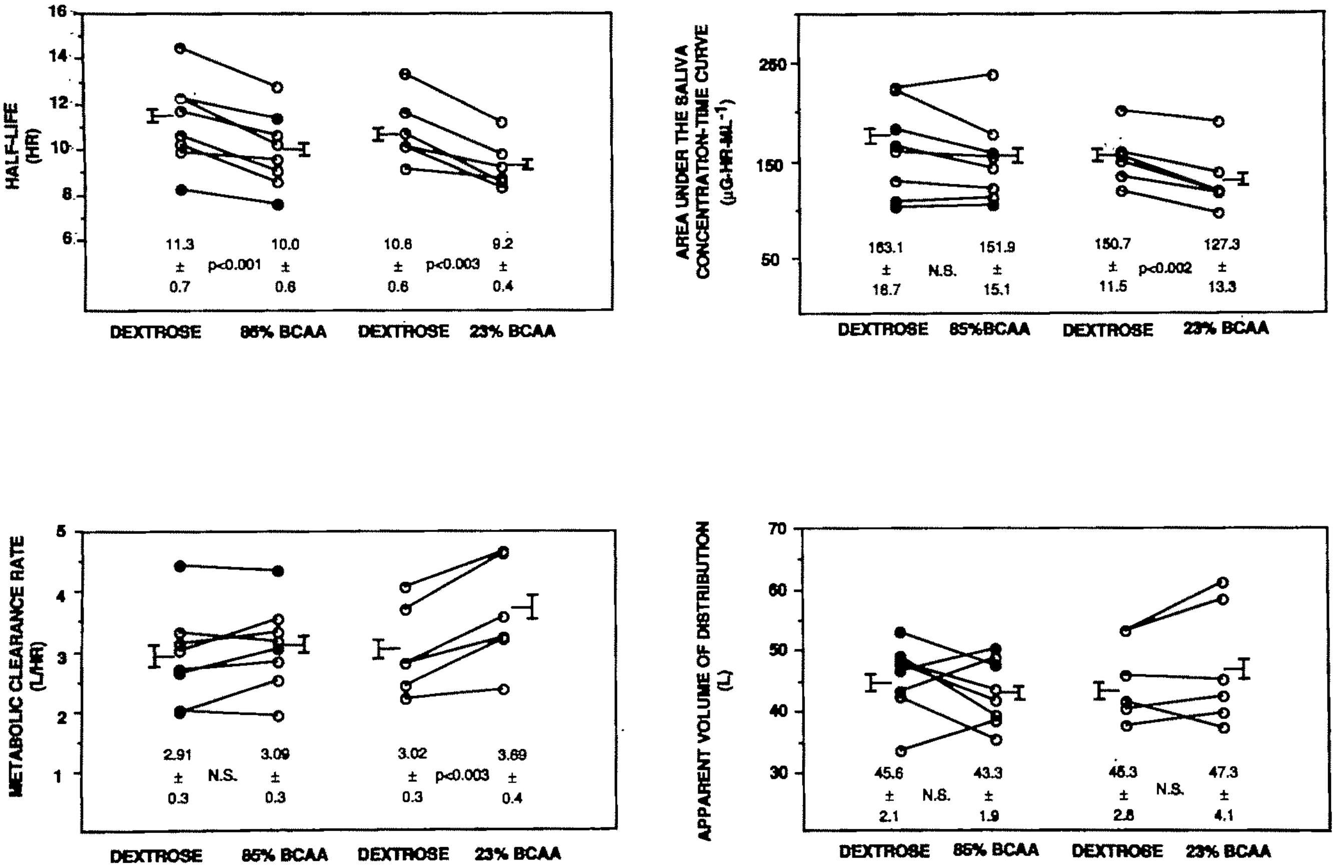

Figure 1. Kinetic values for antipyrine during nutritional regimens. Subjects were given antipyrine 6 mg/kg orally during each intravenous regimen. Values for individual subjects and mean values ± SE are shown. Subjects who did not participate in both studies are indicated by *closed circles*.

calculations were done with use of the computer program PKCALC (23). Results were analyzed statistically by Student's *t*-test for paired data. Differences in mean value were considered statistically significant if P values were <0.05.

Results

Nonlinear regression analysis demonstrated excellent conformity of the log concentration of antipyrine-time curves to a biexponential model under all dietary conditions (mean ± SE of correlation coefficient: dextrose, $n = 8$, 0.975 ± 0.018; 85% branched-chain amino acids, $n = 8$, 0.988 ± 0.007; dextrose, $n = 6$, 0.992 ± 0.005; 23% branched-chain amino acids, $n = 6$, 0.991 ± 0.002). Run analysis of the elimination phase (3–48 h) of the curves was carried out to determine whether the data points deviated systematically from the calculated best fit lines. In only four instances were there deviations of data points from the best fit lines that were nonrandom. In one the data were obtained when a subject was receiving the dextrose infusion, in another the 23% branched-chain amino acid regimen, and in two the 85% branched-chain amino acid solution. Switching from dextrose to the conventional amino acid regimen resulted in a decrease in mean $t_{½}$ for antipyrine ($P < 0.003$), a decrease in mean AUC ($P < 0.002$), an increase in mean MCR ($P < 0.003$), and no significant change in mean aVd (Figure 1). Though there was marked individual variability in the magnitude of the response to the change in nutritional regimen, a decrease in $t_{½}$, a decrease in AUC, and an increase in MCR for antipyrine occurred in all subjects (Figure 1). Switching from dextrose to the branched-chain enriched amino acid regimen decreased mean $t_{½}$ for antipyrine ($P < 0.001$) but did not significantly alter mean AUC, MCR, or aVd (Figure 1).

Switching from dextrose to the conventional amino acid infusion produced no significant alteration in $t_{½}$, AUC, MCR, or aVd of acetaminophen (Table 1). Substituting the branched-chain enriched amino acid regimen for dextrose resulted in a decrease in $t_{½}$ of acetaminophen ($P < 0.05$) accompanied by a decrease in aVd ($P < 0.05$) with no significant alteration in AUC or MCR (Table 1). No

Table 1. Kinetic Values for Acetaminophen and Major Metabolites during Parenteral Nutritional Regimens

Compound	Nutritional regimen Dextrose	Amino acid (23% BCAA)	Dextrose	Amino acid (85% BCAA)
Acetaminophen				
$t_{1/2}$ (h)	3.2 ± 0.2	3.0 ± 0.2	3.1 ± 0.1	2.9 ± 0.1[a]
AUC ($\mu g \cdot h \cdot mL^{-1}$)	85.5 ± 9.9	86.8 ± 9.4	89.4 ± 8.1	93.7 ± 5.3
MCR (L/h)	20.5 ± 2.6	20.1 ± 2.6	19.1 ± 1.5	17.8 ± 1.1
aVd (L)	92.1 ± 7.2	84.4 ± 8.7	83.0 ± 6.0	73.3 ± 3.4[a]
Acetaminophen glucuronide				
AUC ($\mu g \cdot h \cdot mL^{-1}$)	154.4 ± 14.8	151.2 ± 10.6	150.9 ± 13.9	136.9 ± 10.7
Acetaminophen sulfate				
AUC ($\mu g \cdot h \cdot mL^{-1}$)	51.6 ± 5.8	58.9 ± 10.3	54.3 ± 6.6	54.9 ± 7.8

[a] Significantly different from paired dextrose regimen, $P < 0.05$. Subjects were given acetaminophen 1625 mg orally during each intravenous nutritional regimen. Values are mean ± SE for six subjects (conventional amino acid study) or eight subjects (branched-chain enriched amino acid study). AUC = area under curve; aVd = apparent volume of distribution; BCAA = branched-chain amino acids; MCR = metabolic clearance rate; $t_{1/2}$ = half-life.

significant changes in AUC of acetaminophen glucuronide or acetaminophen sulfate resulted from the change to either amino acid regimen (Table 1). Urine collection was incomplete for one subject during both the study in which he received the branched-chain enriched amino acid solution and the study in which he received the conventional amino acid solution, and for another subject during the study in which he received the conventional amino acid solution. No significant alterations in amounts of acetaminophen metabolites excreted in urine occurred after the change to either amino acid regimen (data not shown).

Discussion

While confirming our previous work (8), which showed that in healthy volunteers changing the caloric source of intravenous nutrition from dextrose to a conventional amino acid solution produced an increase in the oxidative metabolism of antipyrine, the results of the present study also show that the increase in oxidative metabolism of antipyrine does not occur when the amino acid solution has a substantially higher branched-chain and substantially lower non-branched-chain amino acid content. In prior studies (1–8,24,25) of the effects of dietary nutrients on oxidative drug metabolizing capacity in humans, alterations in protein intake have been accompanied by changes either in intake of carbohydrate, fat, or total calories. Our data that show that the branched-chain amino acid content of a nutritional regimen composed solely of amino acids influences the effect of the regimen on antipyrine metabolism provide, for the first time, direct evidence that constituents of protein can by themselves enhance human oxidative drug metabolizing capacity.

The slope of the elimination phase (3–48 h) of the log concentration-time curve for antipyrine was greater in all subjects during the 23% branched-chain amino acid regimen than during the preceding dextrose regimen, whereas the monoexponential character of the elimination phase appeared to be unchanged. If the increase in rate of elimination of antipyrine took place between 3 and 48 h after the dose and simultaneous start of the 23% branched-chain amino acid regimen, then the elimination curves would not have been nonexponential over this interval and the data points at one or both ends of the elimination curves would have lain below the calculated best fit lines. Run analysis of the log concentration-time curves for antipyrine was performed to determine whether over the 3–48 h interval data points deviated systematically from the calculated best fit lines. There was only a single instance in which this occurred for data obtained from a subject who was receiving the 23% branched-chain amino acid infusion. These results suggest that the effects of amino acids on antipyrine metabolism occurred soon after the initiation of the infusion. The mechanism by which the substitution of protein for carbohydrate in the human diet enhances oxidative drug metabolizing capacity is not known. It has been suggested that it stimulates the synthesis of specific proteins such as cytochromes P450 that are involved in oxidative drug metabolism (1,2,4,5,26). Such synthesis would be expected to occur gradually over a substantial number of hours (27). Our results raise doubts about whether enhanced protein synthesis could be the underlying mechanism.

Finally, our data show that in healthy individuals an isocaloric change in intravenous nutritional regimen from dextrose, 440 kcal/day, to either a conventional or a branched-chain amino acid enriched amino acid solution for 1 day does not alter the conjugation of acetaminophen. We do not know whether a greater caloric intake of amino acids or a longer period of administration would produce a change in drug conjugation capacity.

In this study, the amino acid nutritional regimen always followed the dextrose nutritional regimen. We do not know whether reversing the order of the regimens would in any way alter the results.

Further work is needed to delineate the effects of parenterally administered nutrients on drug metabolism and the mechanisms by which these effects are produced. Clinicians need to be aware that modifying parenteral nutritional regimens has the potential for altering the effects of ongoing drug therapy.

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References

1. Alvares AP, Anderson KE, Conney AH, Kappas A. Interactions between nutritional factors and drug biotransformations in man. Proc Natl Acad Sci USA 1976;73:2501–4.
2. Kappas A, Anderson KE, Conney AH, Alvares AP. Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. Clin Pharmacol Ther 1976; 20:643–53.
3. Kappas A, Anderson KE, Conney AH, Pantuck EJ, Fishman J, Bradlow HL. Nutrition-endocrine interactions: induction of reciprocal changes in the Δ^4-5α-reduction of testosterone and the cytochrome P-450-dependent oxidation of estradiol by dietary macronutrients in man. Proc Natl Acad Sci USA 1983;80:7646–9.
4. Anderson KE, Kappas A, Conney AH, Bradlow HL, Fishman J. The influence of dietary protein and carbohydrate on the principal oxidative biotransformations of estradiol in normal subjects. J Clin Endocrinol Metab 1984;59:103–7.
5. Juan D, Worwag EM, Schoeller DA, Kotake AN, Hughes RL, Frederiksen MC. Effects of dietary protein on theophylline pharmacokinetics and caffeine and aminopyrine breath tests. Clin Pharmacol Ther 1986;40:187–94.
6. Fagan TC, Walle T, Oexmann MJ, Walle UK, Bai SA, Gaffney TE. Increased clearance of propranolol and theophylline by high-protein compared with high-carbohydrate diet. Clin Pharmacol Ther 1987;41:402–6.
7. Feldman CH, Hutchinson VE, Pippenger CE, Blumenfeld TA, Feldman BR, Davis WJ. Effect of dietary protein and carbohydrate on theophylline metabolism in children. Pediatrics 1980; 66:956–62.
8. Pantuck EJ, Pantuck CB, Weissman C, Askanazi J, Conney AH. Effects of parenteral nutritional regimens on oxidative drug metabolism. Anesthesiology 1984;60:534–6.
9. Ziegenbein RC. Theophylline clearance increase from increased amino acid in a CPN regimen. Drug Intell Clin Pharm 1987;21:220–1.
10. Cerra FB, Mazuski JE, Chute E, et al. Branched chain metabolic support. A prospective, randomized, double-blind trial in surgical stress. Ann Surg 1984;199:286–91.
11. Echenique MM, Bistrian BR, Moldawer LL, Palombo JD, Miller MM, Blackburn GL. Improvement in amino acid use in the critically ill patient with parenteral formulas enriched with branched chain amino acids. Surg Gynecol Obstet 1984; 159:233–41.
12. Vesell ES. The antipyrine test in clinical pharmacology: conceptions and misconceptions. Clin Pharmacol Ther 1979; 26:275–86.
13. Brodie MJ, Boobis AR, Toverud E-L, et al. Drug metabolism in white vegetarians. Br J Clin Pharmacol 1980;9:523–5.
14. Greenblatt DJ, Abernethy DR, Divoll M, Ochs HR, Shader RI. Antipyretic analgesic drugs as models for studies of drug disposition in old age. Am J Med 1983;75:127–32.
15. Bock KW, Wiltfang J, Blume R, Ullrich D, Bircher J. Paracetamol as a test drug to determine glucuronide formation in man. Effects of inducers and of smoking. Eur J Clin Pharmacol 1987;31:677–83.
16. Chang RL, Wood AW, Dixon WR, et al. Antipyrine: radioimmunoassay in plasma and saliva following administration of a high dose and a low dose. Clin Pharmacol Ther 1976;20:219–26.
17. Chang RL, Wood AW, Dixon WR. ^{125}I-Radioimmunoassay for antipyrine. Life Sci 1978;22:855–8.
18. Adriaenssens PI, Prescott LF. High performance liquid chromatographic estimation of paracetamol metabolites in plasma. Br J Clin Pharmacol 1978;6:87–8.
19. Howie D, Adriaenssens PI, Prescott LF. Paracetamol metabolism following overdosage: application of high performance liquid chromatography. J Pharm Pharmacol 1977;29:235–7.
20. Anderson KE, Schneider J, Pantuck EJ, et al. Acetaminophen metabolism in subjects fed charcoal-broiled beef. Clin Pharmacol Ther 1983;34:369–74.
21. Metzler CM, Weiner DL. NONLIN84 User's Guide. Lexington, Ky.: Statistical Consultants, 1984:V.15.
22. Weinberg GH, Schumaker JA. Statistics: an intuitive approach. 3rd ed. Monterey, Calif.: Brooks/Cole, 1974:312–5.
23. Shumaker RC. PKCALC: a BASIC interactive computer program for statistical and pharmacokinetic analysis of data. Drug Metab Rev 1986;17:331–48.
24. Krishnaswamy K, Kalamegham R, Naidu NA. Dietary influences on the kinetics of antipyrine and aminopyrine in human subjects. Br J Clin Pharmacol 1984;17:139–46.
25. Anderson KE, Conney AH, Kappas A. Nutrition and oxidative drug metabolism in man: relative influence of dietary lipids, carbohydrate and protein. Clin Pharmacol Ther 1979;26:493–501.
26. Anderson KE. Influences of diet and nutrition on clinical pharmacokinetics. Clin Pharmacokinet 1988;14:325–46.
27. Parkinson A, Thomas PE, Ryan DE, Levin W. The in vivo turnover of rat liver microsomal epoxide hydrolase and both the apoprotein and heme moieties of specific cytochrome P-450 isozymes. Arch Biochem Biophys 1983;225:216–36.

732 ANESTH ANALG
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In Vitro Study on Mechanisms of Bupivacaine-Induced Depression of Myocardial Contractility

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ELEDJAM JJ, DE LA COUSSAYE JE, BRUGADA J, BASSOUL B, GAGNOL JP, FABREGAT JR, MASSÉ C, SASSINE A. In vitro study on mechanisms of bupivacaine-induced depression of myocardial contractility. Anesth Analg 1989;69:732–5.

Although several mechanisms have been proposed to explain bupivacaine cardiotoxicity, the predominant effect remains to be determined. In this study, we used an isolated rabbit right atrial model that reproduces the effects on inotropic and chronotropic functions induced by 0.5 μg/mL bupivacaine; then we tried to counteract these events by electrical stimulation or by addition of $CaCl_2$ or adenosine triphosphate (ATP) to the bathing solution. Contractile force was dramatically depressed by bupivacaine alone (−68%), even when the preparation was paced (−55%). $CaCl_2$ partially counteracted this decrease (−37%). Inotropic function was almost completely restored (−9%) when ATP was added before administration of bupivacaine. Inhibition of energy metabolism seems to be a major explanation for bupivacaine cardiotoxicity.

Key Words: ANESTHETICS, LOCAL—bupivacaine. HEART, MYOCARDIUM—contractility. TOXICITY—bupivacaine.

The local anesthetic agent bupivacaine is known not only for its potent and long acting action but also for its cardiodepressive effect (1–5). The biophysical properties of the molecule, namely, its high lipid solubility and protein binding, can partly explain this potency and toxicity. These properties are essential features of the pharmacological profile of the drug not only in terms of its bioavailability but also in terms of its mechanism of action (6).

Many in vitro investigations have been performed with bupivacaine, and it is now established that the anesthetic interacts with the fast inward current (3), calcium translocation (5,7), and energy metabolism (6,8). The relative importance of each of these effects in bupivacaine cardiotoxicity has not been established.

The aim of the present study was to evaluate each of these effects on the isolated rabbit right atria and to determine which factor had the most deleterious effect on bupivacaine-induced cardiac depression. For this purpose, the preparation was incubated with a bupivacaine solution at a concentration previously determined in our laboratory to alter contractility. The influence of electrical stimulation and the addition of calcium and adenosine triphosphate (ATP), tested individually, were then evaluated on heart rate and contractile force.

Materials and Methods

To avoid any residual effects of the anesthetic on atrial performance, the rabbits were stunned and then killed by bleeding. The right atrium was excised and bathed, to maintain spontaneous activity, in 200 mL of modified Tyrode's solution composed of NaCl, 145 mM; KCl, 5.6 mM; CaCl, 2.5 mM; glucose, 10.0 mM; and tris(hydroxymethyl)aminomethane, 2.0 mM. The solution was adjusted to pH 7.45, saturated with oxygen, and maintained at 32°C.

Contractile force was measured with use of a microdynamometer fitted with an isometric strain

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Table 1. Stability of Control Preparation Expressed as Percent of Variation from Zero Time

Control group (n = 8)	5 min	10 min	15 min	20 min	30 min	60 min
Spontaneous % decrease	0.5	0.9	0.9	0.9	0.9	0.9
rate SEM	0.5	0.6	0.6	0.6	0.6	0.6
Contractile % decrease	0.1	0	0.3	0	0	0.3
force SEM	0.1	0	0.2	0	0	0.2

gauge (Ugo Basile, MDI 5) and recorded on an oscilloscope (Tektronix, 502 Dual Beam).

The overall study included five experimental groups. Group 1 (n = 8) served to evaluate the stability of the preparation. After a 3-h period to allow the atrial response to become stable, control measurements of spontaneous rate and contractile force were made during the next hour, without any addition of drug. In group 2 (n = 6), after stabilization of the preparation, 0.5 μg/mL of bupivacaine (1.5×10^{-6} M) was added to the Tyrode's solution. In group 3 (n = 6), administration of bupivacaine (0.5 μg/mL) was followed by electrical pacing at a rate 20% faster than the spontaneous atrial rate so as to suppress the frequency-related contractile response. Spikes of 3 ms two times greater in intensity than the diastolic threshold were delivered by a Hugo Sack Electronik Braun Stimulator. In group 4 (n = 6), preparations were incubated in the presence of 7.5 mM $CaCl_2$ for 2 h before addition of 0.5 μg/mL bupivacaine. In group 5 (n = 6), preparations were incubated in the presence of 0.2 mM ATP 30 min before administration of bupivacaine.

In groups 2–6, contractile force and atrial rate were measured immediately before and 5, 10, 15, 20, and 30 min after addition of 1.5×10^{-6} M bupivacaine at time zero.

Each individual measurement was expressed as percent of change with respect to the value at time zero. The significance of the differences between groups was determined by analysis of variance (ANOVA) and Student's t-test for unpaired data. A $P < 0.05$ was considered statistically significant.

Results

Stability of the preparation was assessed in a series of eight control experiments (group 1). As shown in Table 1, the frequency of contraction and the inotropic response remained unchanged for a period of 1 h after the 3-h stabilization period. Having established that our preparation was stable, we proceeded to evaluate the mechanisms involved in bupivacaine-induced cardiotoxicity. The results are presented in Figures 1 and 2.

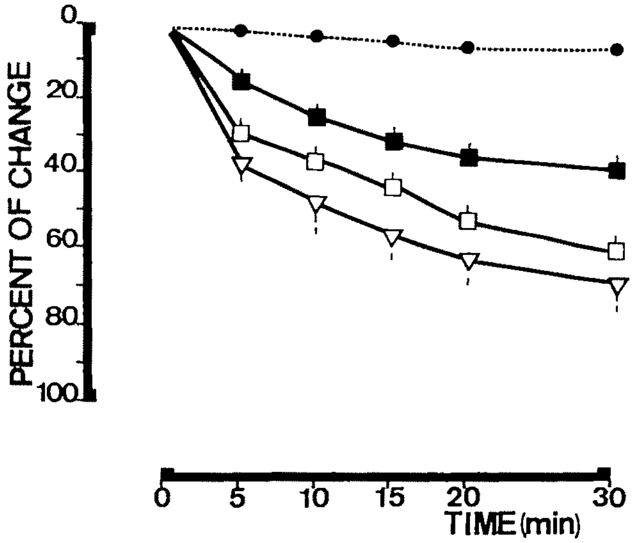

Figure 1. Decreases in contractile force, expressed as percent of contractile force in control preparations (±SEM). ∇ = bupivacaine alone (group 2); □ = bupivacaine followed by electrical pacing (group 3); ■ = bupivacaine added to $CaCl_2$-enriched preparations (group 4); ● = bupivacaine added to preparations pretreated with ATP (group 5).

Bupivacaine at 1.5×10^{-6} M (group 2) significantly depressed the contractile response (68.3 ± 7.0% [SEM] at 30 min) as well as the spontaneous rate of contraction (11.3 ± 2.4% at 30 min). The differences between control group and group 2 were always significant ($0.01 < P < 0.001$), and there was a progressive decay of myocardial contractile force throughout the experimental period. Maximal decrease in rate was reached within 20 min after administration of bupivacaine.

Electrical pacing in group 3 did not counteract the negative inotropic response caused by bupivacaine. There was no significant difference in contractile force between group 3 and group 2 (respectively 59.3 ± 3.0% versus 68.3 ± 7.0%).

In preparations exposed to both bupivacaine and $CaCl_2$ (group 4), changes in contractile response were significant at each time period compared with those of the control group ($0.01 < P < 0.001$). The negative inotropic response, however, was weaker than those recorded on stimulated and nonstimulated prepara-

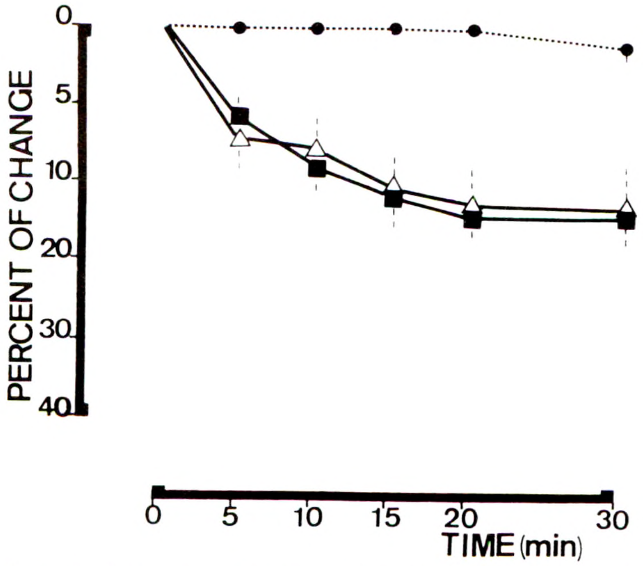

Figure 2. Decrease in spontaneous heart rates expressed as percent of spontaneous heart rate in control preparations (±SEM). △ = bupivacaine (group 2); ■ = bupivacaine added to $CaCl_2$-enriched preparations (group 4); ● = bupivacaine added to preparations pretreated with ATP (group 5).

tions with bupivacaine alone: 37.2 ± 3.9% versus 68.3 ± 7.0% (group 2, $P < 0.01$) or versus 59.3 ± 3.0% (group 3, $P < 0.01$). Changes in spontaneous rate were similar in groups 4 (11.8 ± 1.5%) and 2 (11.3 ± 2.4%).

Addition of ATP, 30 min before addition of bupivacaine (group 5), counteracted the decrease in the spontaneous rate induced by bupivacaine; differences between the control group and group 5 were not significant. In the presence of ATP, there was less decrease in contractile response even though this depression was statistically significant compared with that of the control group ($0.05 < P < 0.01$). Furthermore, differences in contractility and atrial rate in group 5 compared with groups 2, 3, and 4 were highly significant.

Discussion

Bupivacaine at 0.5 μg/mL markedly depressed cardiac function: mechanical performance of the myocardium was decreased by 68% and spontaneous atrial rate by 11% as compared with control values. These results agree with the literature (3,5,9–13) even though the negative inotropic effect was more pronounced in our study. Differences in animal species, nutritive solutions, and calcium concentrations might explain these discrepancies.

Because changes in spontaneous rate are often indicative of cardiac depression, a series of stimulated preparations was studied. Under these conditions, contractile response was similar to that observed in the spontaneously beating atria. Our results are in accordance with those of Clarkson and Hondeghem (3,13) and showed that cardiac depression induced by bupivacaine is not frequency-related. The fact that bupivacaine inhibits the fast (3,13) and the slow inward currents (7) may explain its inhibition of sinus activity (14) and alterations in sinoatrial (4,15), atrial (1,4,15), atrioventricular (1,4,15,16), and ventricular (1,16,17) conduction.

Coyle and Sperelakis (7) demonstrated that bupivacaine inhibits the slow inward current. This blockade could depress calcium-induced calcium release from the sarcoplasmic reticulum (18). In $CaCl_2$-enriched preparations, contractility was partially restored; these results are consistent with those of the previous hypothesis or might be the consequence of a direct inhibitory effect of bupivacaine on sarcoplasmic reticulum as suggested by Lynch (5). However, Tanz et al. (12) failed to reverse the negative inotropic effect of the drug when bupivacaine-treated preparations were exposed to increasing concentrations of calcium. These conflicting results might be explained by the fact that the preparation studied by Tanz et al. (12) was not preincubated with the calcium-enriched solution.

Local anesthetics can inhibit energy metabolism in several ways: blockade of the respiratory chain (19), inhibition of ATPase (20–23), uncoupling of oxidative phosphorylations (6,24), or inhibition of ATP/ADP (adenosine diphosphate) translocation (25,26). Finally, local anesthetics can inhibit Ca-ATPase (27,28). With use of an ATP-enriched solution, both negative inotropic and chronotropic responses to bupivacaine were inhibited: contractile force was only slightly altered compared with that of the control, and spontaneous rate remained unchanged. This powerful cardioprotection with ATP, when compared with that obtained with a calcium-enriched solution, suggests that modification of energy metabolism is a major mechanism of cardiac depression produced by bupivacaine.

In conclusion, the mechanisms of bupivacaine cardiotoxicity, were analyzed in an in vitro model. The results underscored the importance of ATP in preventing the cardiodepressive effect of the drug and showed that interaction between bupivacaine and energy metabolism must be taken into account in explaining the cardiotoxicity of this local anesthetic.

References

1. Hotvedt R, Refsum H, Helgesen KG. Cardiac electrophysiologic and hemodynamic effects related to plasma levels of bupivacaine in the dog. Anesth Analg 1985;64:388–94.

2. Reiz S, Nath S. Cardiotoxicity of local anesthetic agents. Br J Anaesth 1986;58:736–46.
3. Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology 1985;62:396–405.
4. Wheeler DM, Bradley EL, Woods WT. The electrophysiologic actions of lidocaine and bupivacaine in the isolated, perfused canine heart. Anesthesiology 1988;68:201–12.
5. Lynch C. Depression of myocardial contractility in vitro by bupivacaine, etidocaine and lidocaine. Anesth Analg 1986; 65:551–9.
6. Dabadie P, Bendriss P, Erny P, Mazat P. Uncoupling effects of local anesthetics on rat liver mitochondria. FEBS Lett 1987; 226:77–82.
7. Coyle DE, Sperelakis N. Bupivacaine and lidocaine blockade of calcium-mediated slow action potentials in guinea pig ventricular muscle. J Pharmacol Exp Ther 1987;242:1001–5.
8. Cronau LH, Merin RG, Abouleish E, Steenberg M, Melgarejo AB. Functional and metabolic effects of bupivacaine and lidocaine in the perfused working rat heart. Anesth Analg 1988;67:929–35.
9. Block A, Covino BG. Effect of local anesthetic agents on cardiac conduction and contractility. Reg Anesth 1981;6:55–61.
10. Feldman HS, Covino BG, Sage DJ. Direct chronotropic and inotropic effects of local anesthetic agents in the isolated guinea pig atria. Reg Anesth 1982;7:149–56.
11. Sage DJ, Feldman HS, Richard Arthur G, et al. Influence of lidocaine and bupivacaine on isolated guinea pig atria in the presence of acidosis and hypoxia. Anesth Analg 1984;63:1–7.
12. Tanz RD, Heskett T, Loehning RW, Fairfax CA. Comparative cardiotoxicity of bupivacaine and lidocaine in the isolated perfused mammalian heart. Anesth Analg 1984;63:549–56.
13. Clarkson CW, Hondeghem LM. Evidence for a specific receptor site for lidocaine, quinidine and bupivacaine associated with cardiac sodium channels in guinea pig ventricular myocardium. Circ Res 1985;56:496–506.
14. Bosnjak ZJ, Stowe DF, Kampine JP. Comparison of lidocaine and bupivacaine depression of sinoatrial nodal activity during hypoxia and acidosis in adult and neonatal guinea pigs. Anesth Analg 1986;65:911–7.
15. Eledjam JJ, de La Coussaye JE, Brugada J, et al. Cardiac electrophysiological effects of bupivacaine in the anesthetized dog: relation with plasma concentration. Arch Int Pharmacodyn Ther 1988;295:147–56.
16. Komai H, Rusy BF. Effects of bupivacaine and lidocaine on A-V conduction in the isolated rat heart: modification by hyperkalemia. Anesthesiology 1981;55:281–5.
17. Moller RA, Covino BG. Cardiac electrophysiologic effects of lidocaine and bupivacaine. Anesth Analg 1988;67:107–14.
18. Fabiato A. Calcium-induced release of calcium from the cardiac sarcoplasmic reticulum. Am J Physiol 1983;245:C1–C14.
19. Chazotte B, Vanderkooi G. Multiples sites of inhibition of mitochondrial electron transport by local anesthetics. Biochim Biophys Acta 1981;636:153–61.
20. Chazotte B, Vanderkooi G, Chignell D. Further studies on F1 ATPase inhibition by local anesthetics. Biochim Biophys Acta 1982;680:310–2.
21. Laikind PK, Goldenberg TM, Allison NS. On the mechanisms of inhibition of the bovine heart F1 ATPase by local anesthetics. Biochem Biophys Res Commun 1982;109:423–7.
22. Agarwal N, Kalpa VK. Studies on the mechanism of action of local anesthetics on proton translocating ATPase from *Mycobacterium phlei*. Biochim Biophys Acta 1984;764:316–23.
23. Kreschek GC, Adade AB, Vanderkooi G. Differential scanning colorimetry study of local anesthetics effects on F1 ATPase and submitochondrial particles. Biochemistry 1985;24:1715–9.
24. Garlid KD, Nakashima RA. Studies on the mechanism of uncoupling by amine local anesthetics: evidence for mitochondrial proton transport mediated by lipophilic ion pairs. J Biol Chem 1983;258:7974–80.
25. Spencer TL, Bygrave FL. Inhibition by local anesthetics of adenine nucleotide translocation in rat liver mitochondria. Biochem J 1974;140:413–22.
26. Fayle DR, Baritt GL, Bygrave FL. The effect of butecaine on adenine nucleotide binding and translocation in rat liver mitochondria. Biochem J 1975;148:527–31.
27. Lavoie PA, Mekhail JK, Sharkawi M. Biphasic effect of local anesthetics on the adenosine triphosphate dependent calcium uptake by lysed brain synaptosomes. Can J Physiol Pharmacol 1986;64:218–21.
28. Garcia-Martine E, Guttierres-Merino C. Local anesthetics inhibit the Ca2+, Mg2+-ATPase activity of rat brain synaptosomes. J Neurochem 1986;47:668–72.

Disposition Kinetics of Ropivacaine in Humans

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The pharmacokinetic characteristics of a new local anesthetic drug, ropivacaine, were determined after intravenous infusion of 50 mg of the hydrochloride salt into six healthy male volunteers. Results showed that the disposition of ropivacaine can be described by a biexponential function. Its blood clearance (0.72 ± 0.16 L/min) is intermediate between that of mepivacaine and bupivacaine. Plasma binding averaged 94% ± 1% and the volume of distribution at steady state based on blood drug concentration was 59 ± 7 L. The terminal elimination half-life was 111 ± 62 min.

Key Words: ANESTHETICS, LOCAL—ropivacaine. PHARMACOKINETICS—ropivacaine.

Ropivacaine (*S*-(-)-1-propyl-2′,6′-pipecoloxylidide hydrochloride monohydrate), an amide-type local anesthetic, is the *N*-propyl homologue of bupivacaine and mepivacaine (Figure 1). It is used in water-soluble form as the hydrochloride monohydrate salt. In contrast to bupivacaine and mepivacaine, which are used as racemates, ropivacaine has been developed as the levoisomer. Animal experiments have shown ropivacaine to be less toxic than bupivacaine after intravenous (IV) administration (1). In particular, the ratio between lethal and convulsive doses is higher with ropivacaine than it is with bupivacaine, and ropivacaine is less potent than bupivacaine at inducing cardiac arrhythmias (Astra Pharmaceuticals AB, Södertälje, Sweden; personal communication). As a prelude to comparing the toxicity of ropivacaine and bupivacaine in humans, a low-dose pharmacokinetic study was carried out to elucidate its disposition kinetics.

Methods

Six healthy male volunteers, aged 19–34 yr, took part in the study, which was approved by the local ethics committee. Written informed consent was obtained. The height of the subjects ranged from 172 to 187 cm and their weights were between 65 and 87 kg. All subjects were in the normal weight range for their height. Alcohol, caffeine-containing drinks, and cigarettes were not allowed during the study or for 24 h before it began.

A control blood sample and an initial 12-lead electrocardiogram were obtained before 50 mg (10 mL) of ropivacaine hydrochloride monohydrate as a 0.5% wt/vol solution was infused intravenously at a constant rate, using a Harvard infusion pump, over 15 min (0.67 mL/min). Venous blood (10 mL) was withdrawn from the opposite arm 5, 10, 15, 16, 20, 25, 30, 35, 40, 50, 60, 90, and 120 min and 4, 6, 12, 24, and 25 h after the start of the infusion. The plasma was separated immediately by centrifugation and stored in glass tubes at −20°C until assay. Additional 5-mL blood samples were taken at 16 and 30 min to measure the whole-blood drug concentrations and the extent of plasma protein binding. Heart rate, blood pressure, and 12-lead electrocardiograms were recorded at 5-min intervals for 30 min. In addition, the subjects were monitored continuously using a Roche 125 electrocardiograph. Symptoms or signs of toxicity were recorded.

Plasma and whole blood concentrations of ropivacaine were measured by a gas chromatographic method using a nitrogen-sensitive detector with a precision of 8% at 1 μg/mL. The minimum assayable concentration was 10 ng/mL. Plasma protein binding

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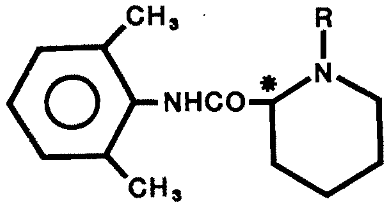

Figure 1. Chemical structure of ropivacaine compared with mepivacaine and bupivacaine. An *asterisk* denotes an asymmetric carbon atom. Ropivacaine, R = n-C_3H_7; mepivacaine, R = n-CH_3; bupivacaine, R = n-C_4H_9. Ropivacaine has been developed as a single enantiomer (levoisomer), whereas mepivacaine and bupivacaine are used as racemates.

was measured using an ultrafiltration technique (Amicon Micropartition System) at 37°C, with mean plasma ropivacaine concentrations of 1.43 ± 0.40 and 0.92 ± 0.17 μg/mL at 16 and 30 min, respectively. Ultrafiltration was preferred to equilibrium dialysis as less than 0.1% of radiolabeled ropivacaine binds to the membrane at the concentrations involved.

Drug concentration-time ($C_{(t)}$) profiles during and after infusion were fitted by Equation (1) using the NONLIN program (2). Concentrations were weighted by the reciprocal of their squared values.

Equation (1) is as follows:

$$C_{(t)} = \frac{R_0}{V_1}\left[\frac{(1 - e^{\lambda_1\tau})\cdot C_1e^{-\lambda_1 t}}{-\lambda_1} + \frac{(1 - e^{\lambda_2\tau})\cdot C_2e^{-\lambda_2 t}}{-\lambda_2}\right], \quad (1)$$

where τ = infusion time, R_0 = infusion rate, and V_1 = initial volume of distribution.

Values of various pharmacokinetic parameters were calculated from the coefficients (C_1, C_2) and exponents (λ_1, λ_2), which are terms of Equation (1) using standard equations (3). All results were expressed as mean ± SD.

Results

None of the subjects had any symptoms or signs of systemic toxicity, and there were no significant alterations in heart rate, blood pressure, or electrocardiograms during the study.

Concentrations of ropivacaine in plasma samples collected more than 6 h after the start of infusion of 50 mg of ropivacaine could only be detected in one subject. The peak plasma concentration ranged between 1073 and 2048 ng/mL, with a mean of 1503 ± 362 ng/mL. The mean parainfusion and postinfusion plasma concentration–time profile of ropivacaine (Figure 2) was well described by Equation (1) as assessed by the "goodness-of-fit" criteria of Boxenbaum et al. (4).

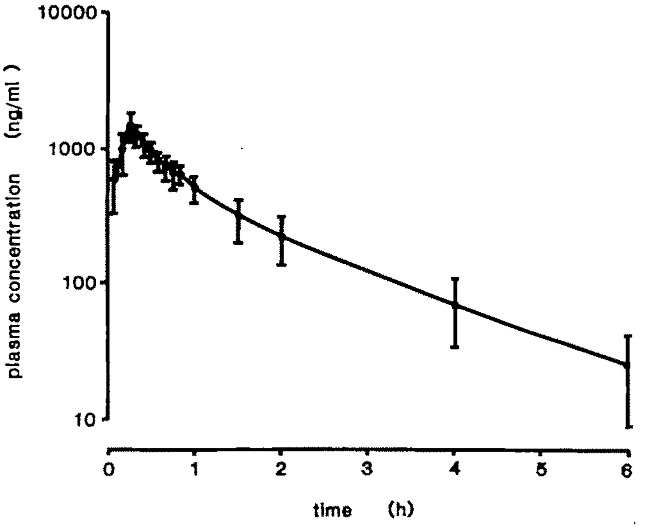

Figure 2. Mean (±SD) venous plasma concentrations of ropivacaine (base) over 6 h after starting a constant-rate IV infusion in six subjects (50 mg of ropivacaine hydrochloride given over 15 min).

Derived pharmacokinetic parameters are shown in Table 1 together with the mean blood/plasma drug concentration ratio and the mean free fraction of drug in plasma. The volume of distribution of unbound drug (Vu_{ss}) was calculated by dividing plasma V_{ss} values by the free fraction of drug in plasma for each individual subject and is also given in Table 1. The mean terminal elimination half-life ($t_{1/2}$) was 111 ± 68 min and the mean plasma and blood clearances were 0.50 ± 0.12 and 0.72 ± 0.16 L/min, respectively. The volume of distribution at steady state based on blood drug concentration (V_{ss}) was 59 ± 7 L. The mean extent of plasma protein binding was high, 94% ± 1%, with a blood/plasma concentration ratio of 0.690 ± 0.059.

Discussion

Ropivacaine is less lipid-soluble than bupivacaine (5), but would be expected to be more lipid-soluble than its *N*-methyl homologue mepivacaine. Predictably, therefore, as compared with bupivacaine and mepivacaine, it has intermediate values of unbound volume of distribution at steady state (Vu_{ss}) and blood clearance (Table 2). The former parameter is a better index of tissue binding than the volume of distribution based on the total drug concentration (V_{ss}) in blood, which is more influenced by offsetting differences in plasma binding (5). The major part of ropivacaine in whole blood is associated with the plasma proteins. The extent of protein binding in plasma was very similar to that of bupivacaine (Table 2), and most of

Table 1. Pharmacokinetic Parameters for Ropivacaine in Humans

Variable		Mean	SD
Exponents of equation describing plasma drug concentration–time profile	λ_1 (L/min)	0.357	0.047
	λ_2 (L/min)	0.0079	0.0035
Coefficients of equation describing plasma drug concentration–time profile	C_1 (ng/mL)	1354	510
	C_2 (ng/mL)	482	350
Terminal half-life	$t_{1/2,z}$ (min)	111	62
Plasma clearance	Cl (L/min)	0.50	0.12
Blood clearance	Cl_b (L/min)	0.72	0.16
Volume of distribution at steady state (based on total plasma drug concentration)	V_{ss} (L)	42	5
Volume of distribution at steady state (based on unbound drug concentration)	Vu_{ss} (L)	742	94
Free fraction in plasma	fu	0.06	0.01
Blood/plasma concentration ratio	$K_{b/p}$	0.590	0.059
Volume of distribution at steady state based on blood drug concentration	$V_{ss,b}$	59	7

Table 2. Pharmacokinetic Parameters Describing the Disposition of Mepivacaine, Bupivacaine, and Ropivacaine in Humans

Variable	Mepivacaine	Bupivacaine	Ropivacaine
$t_{1/2,z}$ (min)	114	162	111
Cl_b (L/min)	0.78	0.58	0.73
$V_{ss,b}$ (L)	84	73	59
Vu_{ss} (L)	382	1028	678
Protein binding (%)	78	96	94
$K_{b/p}$	0.92	0.73	0.69

Data for mepivacaine and bupivacaine are from Tucker (6).

Clearance values refer to whole blood clearance. Volumes of distribution are specified with respect to arterial sampling for mepivacaine and bupivacaine and peripheral venous sampling for ropivacaine.

this binding is accounted for by association with α_1-acid glycoprotein. The present data show that clearance of ropivacaine appears to be closer to that of mepivacaine than to that of bupivacaine, suggesting an intermediate hepatic extraction ratio and, therefore, a dependence of its elimination on both liver blood flow and enzyme activity (6). Similarly, the terminal $t_{1/2}$ of the two lower homologues appears to be less than that of bupivacaine (Table 2), reflecting differences in the balance between clearance and distribution, but also, possibly, differences in the ability to calculate the terminal elimination phase accurately as a result of analytical insensitivity.

All of the above observations on the relative pharmacokinetics of the agents must also be qualified by the fact that a single isomer (ropivacaine) is being compared with racemates (mepivacaine, bupivacaine), and there may be appreciable stereoselectivity in disposition processes.

Knowledge of the disposition kinetics of ropivacaine will assist in the design of safe IV infusion regimens to assess the threshold toxicity of the drug in humans, to evaluate its systemic uptake from various perineural sites after single, multiple, or continuous dosage, and to estimate its therapeutic index.

Gorel Osterlof is acknowledged for ropivacaine analysis.

References

1. Akerman B, Hellberg I-B, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Acta Anaesthesiol Scand 1988;32:571–8.
2. Metzler CM, Elfring GK, McEwen AJ. A package of computer programs for pharmacokinetic modelling. Biometrics 1974; 30:562–3.
3. Gibaldi M, Perrier D. Pharmacokinetics. London: Marcel Dekker, 1982.
4. Boxenbaum HG, Riegelman S, Elashoff RM. J Pharmacokinet Biopharm 1974;2:123–48.
5. Rosenberg PH, Kytta J, Alila A. Absorption of bupivacaine, etidocaine, lignocaine and ropivacaine into n-heptane, rat sciatic nerve, and human extradural and subcutaneous fat. Br J Anaesth 1986;58:310–4.
6. Tucker GT. Pharmacokinetics of local anaesthetics. Br J Anaesth 1986;58:717–31.

Motor and Sensory Blockade after Epidural Injection of Mepivacaine, Bupivacaine, and Etidocaine—A Double-Blind Study

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AXELSSON K, NYDAHL P-A, PHILIPSON L, LARSSON P. Motor and sensory blockade after epidural injection of mepivacaine, bupivacaine, and etidocaine—a double-blind study. Anesth Analg 1989;69:739–47.

In a double-blind study of epidural anesthesia, 30 young volunteers were given either 2% mepivacaine (400 mg), 0.5% bupivacaine (100 mg), or 1.5% etidocaine (300 mg), all solutions containing epinephrine (1:200,000). The spread of analgesia was equal in the groups, whereas the longest duration was noted in the etidocaine and bupivacaine groups. With use of a method for determining muscle force, motor blockade during anesthesia was recorded quantitatively for hip flexion, knee extension, and plantar flexion of the big toe. Onset of motor blockade was significantly more rapid with etidocaine than with bupivacaine and mepivacaine. All subjects given etidocaine developed complete motor blockade, but with the other local anesthetics 5%–33% of the initial muscle force remained. The least motor blockade was found in the L5-S2 segment (plantar flexion of the big toe). The duration of maximal motor blockade varied between 60 min (mepivacaine) and 360 min (etidocaine). With each of the three local anesthetics, motor function returned simultaneously in the three muscle groups tested. Complete restoration of muscle function occurred significantly later for etidocaine (600 min) than for bupivacaine (360 min) and mepivacaine (180 min). With etidocaine, the motor blockade outlasted the sensory blockade by 150 min. The Bromage scale corresponded to the motor blockade only during the first half of the regression phase. Not until 1–3 h after attainment of Bromage grade 0 was the muscle force of all movements restored (90% of control values).

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL. ANESTHETICS, LOCAL—mepivacaine, bupivacaine, etidocaine.

High concentrations of local anesthetics are required to produce both sensory and motor blockade during epidural anesthesia (1). However, with certain local anesthetics, given epidurally, there seems to be a poor correlation between the degrees of motor and sensory blockade (2–5) when motor blockade is estimated with use of the Bromage scale (6). Motor blockade can, however, quantitatively be measured by dynamometry or by isometric muscle force methods more accurately than by the Bromage scale both during onset of anesthesia and during the entire regression phase (7,8). Application of this method to studies during spinal anesthesia has shown that the Bromage scale reflects only the first half of the regression phase of the motor blockade (9,10), i.e., when the motor blockade is still pronounced.

The aims of the present investigation were, first to quantify the motor blockade in subjects given one of three commonly used local anesthetics epidurally (mepivacaine, bupivacaine, or etidocaine, all with epinephrine), and, second, to relate the quantitatively obtained values of motor blockade to measurements made with use of the Bromage scale and to compare the dermatomal levels of sensory and motor blockade during the regression phase.

Materials and Methods

The volunteers in this study had no spinal deformities or mental or neurological disorders and were of comparable age (19–34 yr), height (167–188 cm), and weight (62–93 kg). They gave consent after being given verbal and written information about the study, which was approved by the Ethics Committee at the Örebro Medical Center Hospital. The subjects were divided randomly by a double-blind procedure

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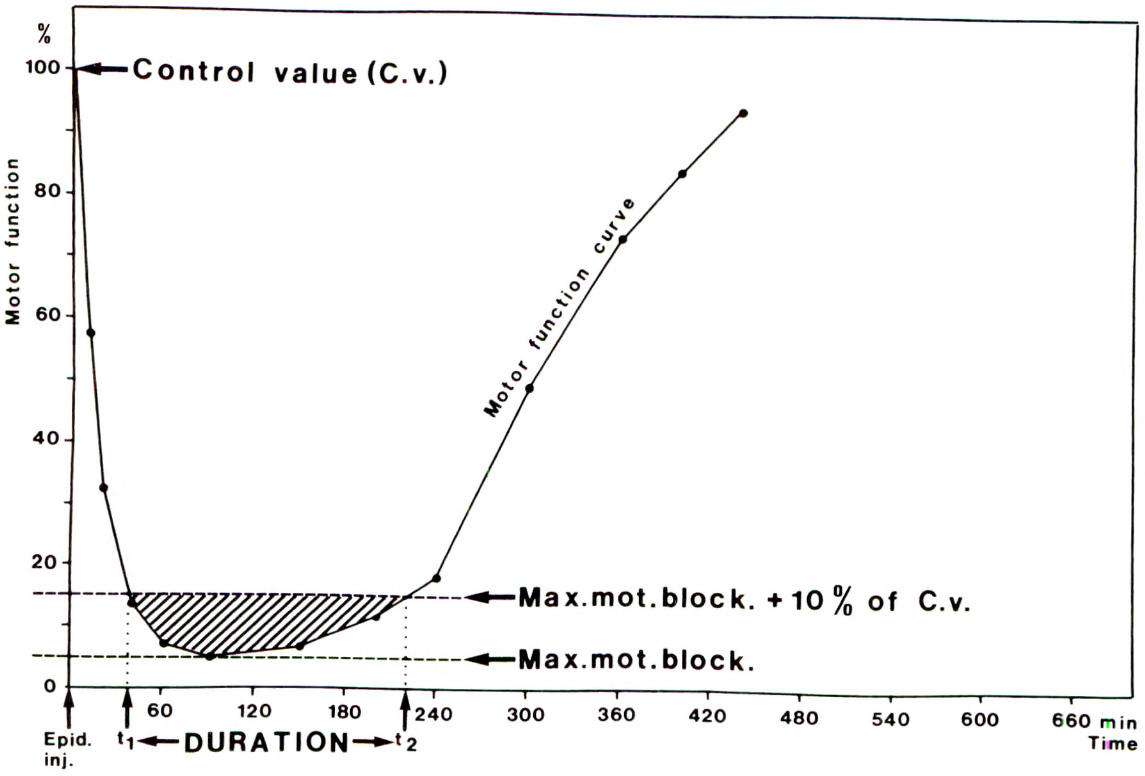


Figure 1. The duration of maximal motor blockade was estimated as the difference between the two calculated times t_1 and t_2 for each muscle group.

into three groups of 10, each group to receive one of the three test drugs. All subjects were give 20 mL of either 2% mepivacaine (400 mg), 0.5% bupivacaine (100 mg), or 1.5% etidocaine (300 mg), all solutions containing epinephrine 1:200,000. No premedication was given apart from 0.5% atropine IV just before the epidural injection. The epidural injection was performed with a 16-gauge Tuohy needle with the subject in a horizontal lateral position, with use of the loss of resistance method at the L2-3 interspace. A 4-mL test dose was given and 2 min were allowed to elapse before the remaining 16 mL of the solution was injected in a single bolus. All subjects were given 500 mL of lactated Ringer's solution IV before the lumbar epidural injection.

In the 30 healthy male volunteers, muscle force measurements were performed before epidural injection and during onset and regression of the epidural anesthesia with use of the methods described elsewhere (8). The maximal isometric forces achieved during knee extension, hip flexion, and plantar flexion of the big toe were recorded by force transducers. Measurements were made in both legs simultaneously with the subject in the lithotomy position. The error of the method has been found to be 10% (8).

A set of tests consisted of maximal muscle contractions affecting the joints mentioned previously, performed five times. The mean of the measurement values for each type of contraction was then calculated for the left and the right side separately. After the epidural injection, the measurements were repeated until the motor blockade was complete or until a steady state had been reached. In the regression phase, repeated muscle force measurements were performed every 30–45 min. The mean isometric force of each movement was expressed in percent of the control value (the mean value of four sets of tests before administration of epidural anesthesia). The continuous time-course of the motor blockade in each subject was estimated by means of linear interpolation between measurements. To compare the motor blockade in the three groups, times were calculated for each measurement site (hip, knee, and big toe) for 25%, 50%, 75%, and 90% of the control value during the onset and regression phases. The duration of maximal motor blockade was estimated as the difference between the two calculated times, t_1 and t_2, for each muscle group as shown in Figure 1. The muscle force of the lower extremities was considered to be completely restored when at least 90% of the initial force values had been regained during the regression phase. The degree of motor blockade was also assessed according to the modified Bromage scale (0–3), with use of the following scoring: 0 = no paralysis (full flexion of knees and feet); 1 = inability to raise extended leg (just able to move knees); 2 = inability to flex knee (able to move feet only); 3 = inability to flex ankle joint (unable to move feet or knees). The level of analgesia during onset was determined repeatedly with use of the pin-prick method, until maximal caudal and cephalad spread of the analgesia had been attained. Similar recordings were made every 15–30 min during regression of sensory and motor blockade, including each of the five muscle force measurements.

Statistics

One-way analysis of variance and Scheffé's test were used to test the differences between the local anesthetic groups. To compare values for the left and right side (sensory and motor blockade), Student's *t*-test for dependent samples was used. $P \leq 0.05$ was adopted as the level of statistical significance.

Results

Sensory Blockade

There was no significant difference in the time from injection to onset of analgesia between the mepivacaine and bupivacaine groups. Etidocaine, however, had a significantly shorter onset time than that of bupivacaine at the L5 segment (15 ± 1.5 min for etidocaine; 28 ± 4.0 min for bupivacaine; mean ± SD). All subjects had a level of analgesia of at least T12 (mepivacaine, bupivacaine) and L1 (etidocaine) (Figures 2a–4a). In the bupivacaine group, dermatomes in the L5-S2 region did not become anesthetized in three subjects (Figure 3a). The duration of analgesia was significantly longer with bupivacaine and etidocaine than with mepivacaine in the T12-S5 area. Even though etidocaine had a significantly longer duration than that of bupivacaine in the L4 and S3-S5 areas, the time from epidural injection to complete regression of the sensory blockade did not differ between these two solutions.

Motor Blockade—Quantitative Method: Onset

The onset of motor blockade was significantly more rapid for hip flexion and knee extension than that for plantar flexion of the big toe, irrespective of the local anesthetic used (Figures 2b–4b). For example, in the

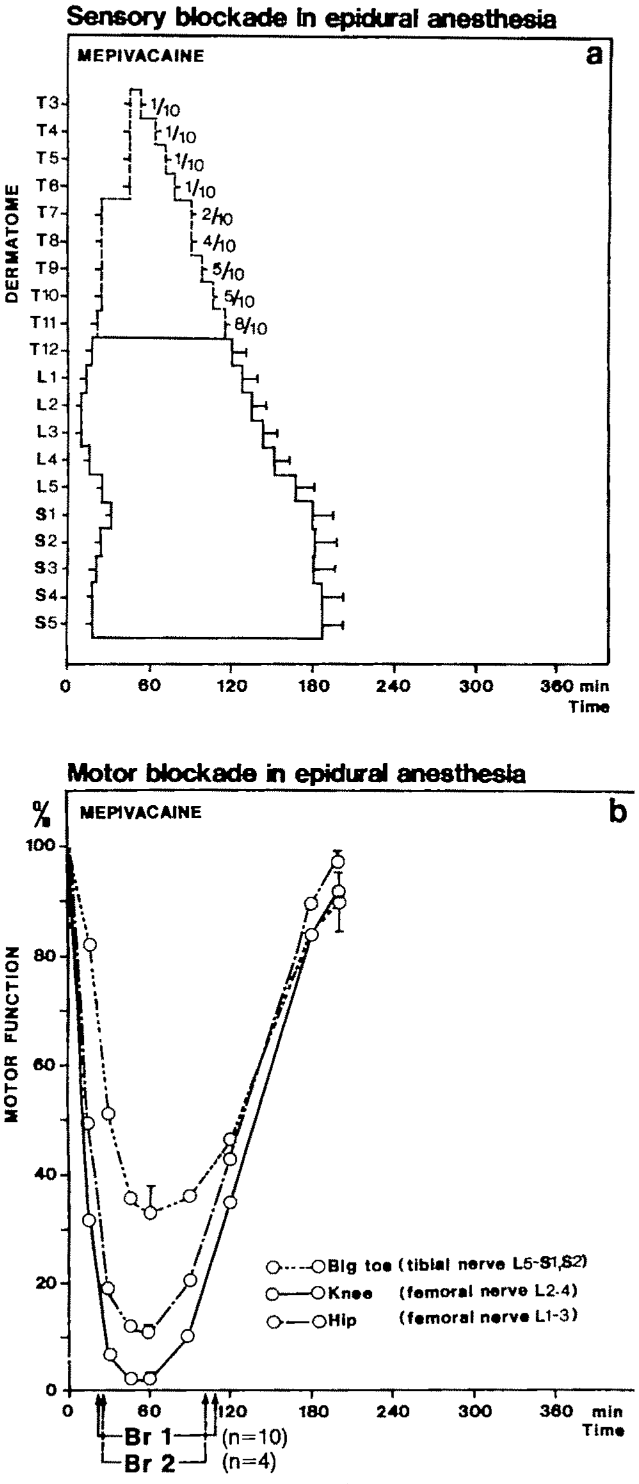


Figure 2. (a), Segmental spread and duration of analgesia (mean ± SEM) after epidural injection of 20 ml of 2% mepivacaine with epinephrine. The upper level of analgesia was T12 in *all* subjects. (b), Onset and regression of motor blockade in the mepivacaine group. Different degrees of Bromage grade are indicated. Bromage grade 3 (only one patient) is excluded. When Bromage changed from grade 1 to grade 0 during regression, the muscle force had returned to <40% of the control value.

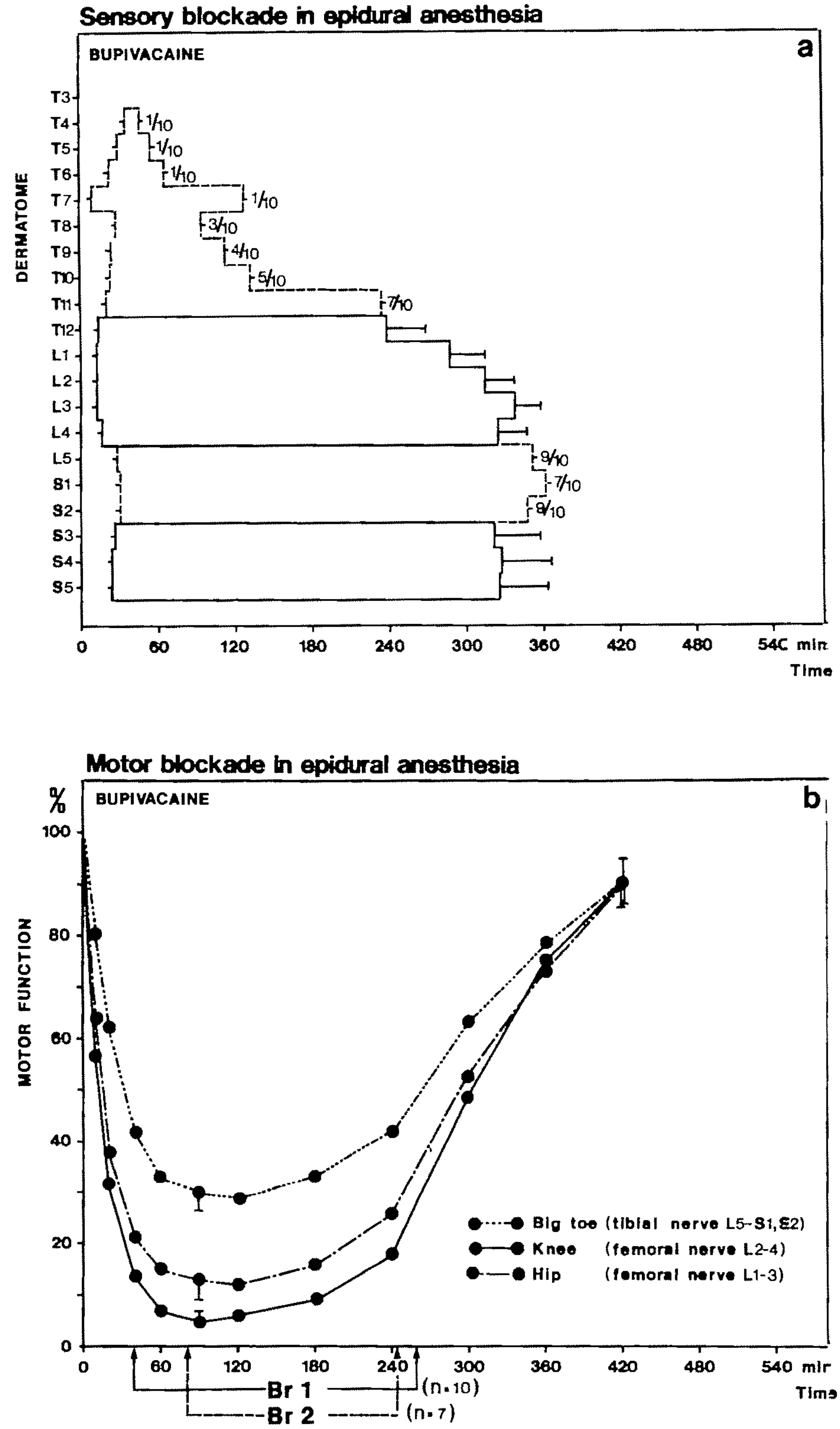


Figure 3. (a), Segmental spread and duration of analgesia (mean ± SEM) after epidural injection of 20 mL of 0.5% bupivacaine with epinephrine. The upper level of analgesia was T12 in *all* subjects. Segments were missing in three subjects—one the L5-S2 segment and the other two the S1 segment. (b), Onset and regression of motor blockade in the bupivacaine group. None of the contraction types showed complete motor blockade. The muscle force started to return roughly at the same time. Bromage grade 3 (only one patient) is excluded. At Bromage grade 0 there was a considerable degree of motor blockade.

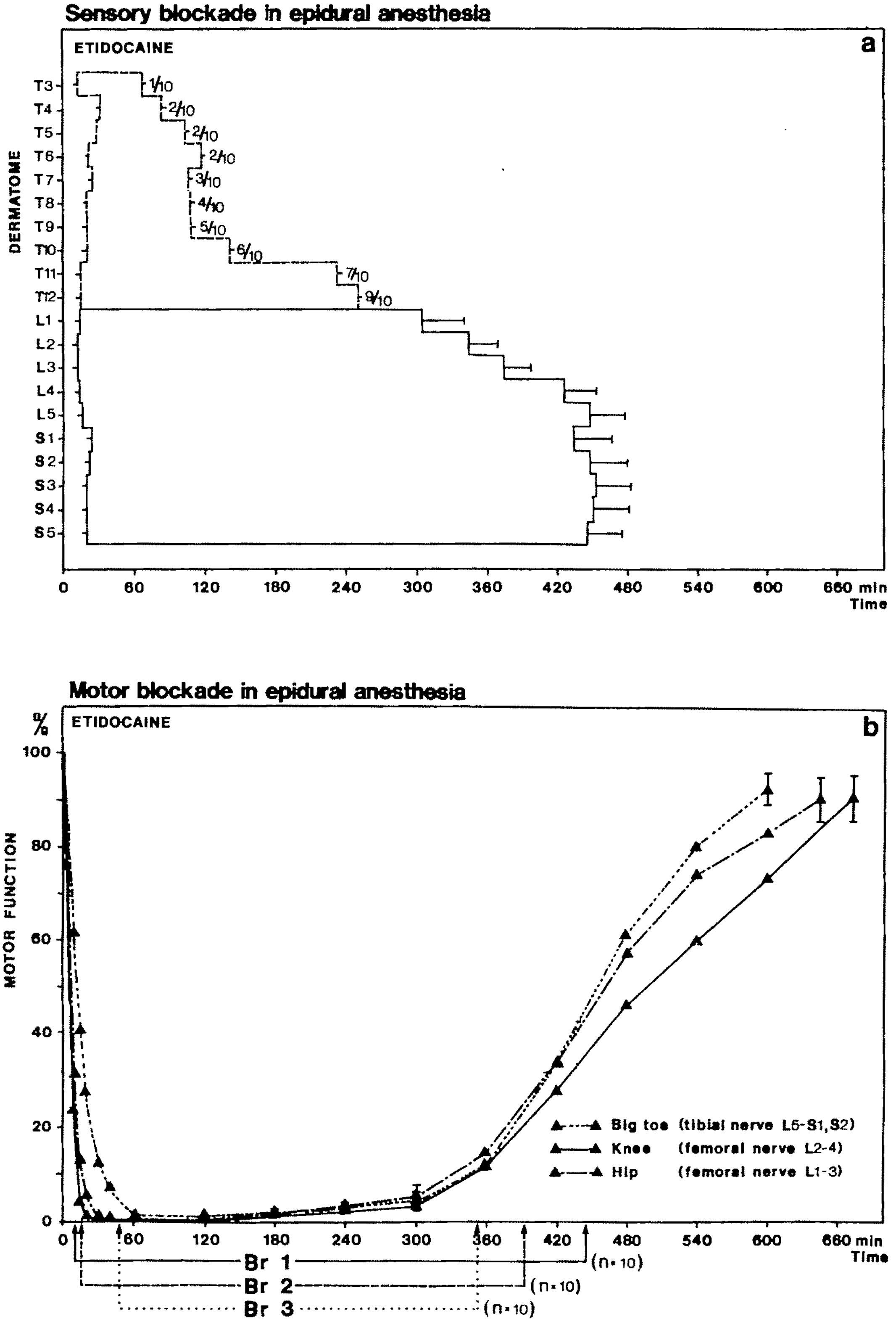
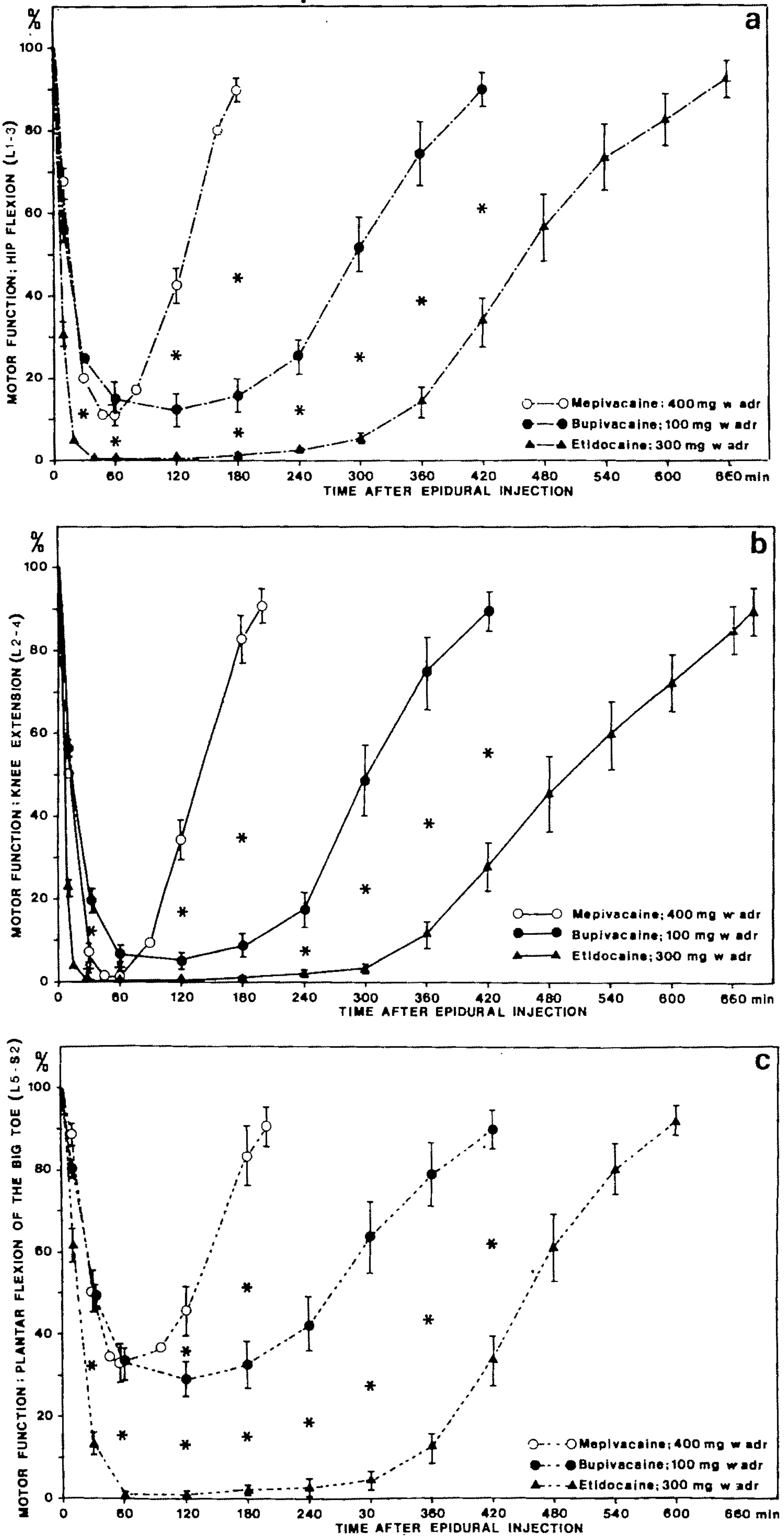


Figure 4. (a), Segmental spread and duration of analgesia (mean ± SEM) after epidural injection of 20 ml of 1.5% etidocaine with epinephrine. The upper level of analgesia was L1 in *all* subjects. (b), Onset and regression of motor blockade in the etidocaine group. Ther was complete motor blockade in all three measurement sites. The muscle force started to return almost at the same time. About 3 h afte Bromage grade 0 the muscle force had returned to 90% of the control value.

Motor blockade in epidural anesthesia



mepivacaine group, muscle force was reduced to 75% of the control value for hip flexion and knee extension within 6–8 min after the epidural injection and for plantar flexion of the big toe 20 min after the injection (Figure 2b).

The onset of motor blockade was significantly more rapid in the etidocaine group than in subjects given mepivacaine and bupivacaine. Thus, the isometric muscle force of knee extension/hip flexion and plantar flexion of the big toe was reduced to 50% of the control value 6 and 14 min after the epidural injection in the etidocaine group, but not until 13 and 30 min in the bupivacaine group and 11 and 28 min, respectively, in the mepivacaine group (Figure 5).

Degree of Motor Blockade

Complete motor blockade was achieved in all subjects given etidocaine. In the other two groups, between 2% and 33% of the initial isometric muscle force persisted. There was a significant difference in the degree of motor blockade between the etidocaine and the other two groups (Figure 5).

Duration and Regression of the Motor Blockade

The duration of maximal motor blockade (Figure 1) was significantly longer in the etidocaine (346–389 min; Figure 4b) than in the bupivacaine group (160–190 min; Figure 3b). The subjects who received mepivacaine had the shortest duration (57–75 min; Figure 2b). During regression, the isometric muscle force returned at the same time in the knee, hip, and the big toe in each group (Figures 2b–4b).

The muscle force returned significantly more slowly in the etidocaine group than in the bupivacaine group ($P < 0.001$) and was regained significantly later in the bupivacaine group than in the mepivacaine group ($P < 0.001$). The length of time between epidural injection and complete regression of the motor blockade (90% of the control value) was 180 min for mepivacaine, just over 360 min for bupivacaine, and just over 600 min for etidocaine, i.e., the ratio for the duration of motor blockade of mepivacaine to bupivacaine to etidocaine was roughly 1:2:3.

Bromage Scale and Its Relation to the Method of Isometric Muscle Force Measurement

The time to reach taken bilateral Bromage grade 1 was significantly shorter after administration of etidocaine (mean ± SD: 10 ± 4.0 min) than it was with bupivacaine (37 ± 21.0 min; $P < 0.01$). In the mepivacaine group, this time was 21 ± 10.4 min. The difference between etidocaine and mepivacaine was not significant.

The degree of motor blockade was greatest in the etidocaine group. All patients in this group had complete motor blockade in the lower limbs, compared with only one patient in each of the other two local anesthetic groups. The duration of motor blockade of Bromage grade 1 (Figures 2b–4b) was around 1.5 h in the mepivacaine, almost 4 h in the bupivacaine, and just over 7 h in the etidocaine group. The differences in duration between the groups were significant. During onset, when the Bromage scale changed from grade 0 to grade 1, 50%–75% of the isometric force remained for plantar flexion of the big toe and only 25%–50% for knee extension and hip flexion (Figures 2b–4b).

According to the Bromage scale, seven patients had almost complete motor blockade (Bromage grade 2) in the bupivacaine group and four patients in the mepivacaine group. With the isometric quantitative method, there was no significant difference in the degree of motor blockade between the two groups investigated; 5%–29% of the initial muscle force remained in the bupivacaine group and 2%–33% in the mepivacaine group.

During regression, when the Bromage scale changed from grade 1 to 0, 25%–30% of the initial muscle force was observed for hip flexion and knee extension in the mepivacaine group, whereas the corresponding figures for the bupivacaine and etidocaine groups were 35%–45% (Figures 2b–4b). For plantar flexion of the big toe, 40% (mepivacaine group) to 55% (bupivacaine group) of the muscle force had returned. Not until 60 min (mepivacaine group) to 180 min (etidocaine group) after attainment of grade 0 on the Bromage scale was the motor blockade considered to have completely regressed (Table 1).

Figure 5. Comparison of the three local anesthetic solutions with respect to degree of motor blockade (mean ± SEM; $^*P \leq 0.05$) at different times after epidural injection: (a), Hip flexion. There was partial motor blockade in the mepivacaine group. The motor blockade curves flattened out increasingly for the long-lasting solutions. (b), Knee extension. There was almost complete motor blockade with all local anesthetics. (c), Plantar flexion of big toe. Although all subjects but one in the mepivacaine and bupivacaine groups were able to move their toes, there was a considerable reduction in the muscle force.

Table 1. Time Taken for Complete Regression of Motor Blockade (90% of control value) and Sensory Blockade

Complete regression of	Mepivacaine	Bupivacaine	Etidocaine
Bromage scale (Br 0)^{a}	107 ± 31.8	257 ± 22.3^{b}	443 ± 28.4^{c}
Motor blockade			
Isometric method (90% of control value)	182 ± 37.2	392 ± 102.6^{b}	622 ± 137.4^{c,d}
Analgesia	187 ± 41.7	367 ± 132.7	453 ± 93.3

Values are mean ± SD, in minutes.

Differences are significant for the following: [a]Bromage scale vs isometric method, irrespective of local anesthetics; [b]0.5% bupivacaine vs 2% mepivacaine; [c]1.5% etidocaine vs other solutions; and [d]motor blockade with isometric method vs sensory blockade.

Sensory Blockade (pin-prick) and Its Relation to Motor Blockade

At the beginning of the regression of motor blockade for hip flexion (innervation L1-3), knee extension (innervation L2-4), and plantar flexion of the big toe (L5-S2), the sensory blockade still remained at L1-S5 in the mepivacaine and bupivacaine groups and at L2-S5 in the etidocaine group. There were no significant differences in times between the complete regression of sensory and motor blockades (90% of the control value) in the bupivacaine and mepivacaine groups. In the etidocaine group, only 40% of the muscle force had returned by the time that the sensory blockade had completely regressed (Figure 4). The difference in time between complete regression of sensory and motor blockade in the etidocaine group was 2.5 h and statistically significant (Table 1). As shown in Table 1 in the mepivacaine and bupivacaine groups, complete regression of sensory blockade occurred significantly later than that of motor blockade as recorded by the Bromage scale. In the etidocaine group, there was no significant time difference between complete regression of sensory blockade and of motor blockade (Bromage scale).

Mobilization

The volunteers were mobilized when the muscle force had reached 90% of the control value at all measurement sites, bilaterally. After an average of about 4 h (3–5 h), the subjects in the mepivacaine group were mobilized. In the bupivacaine and etidocaine groups, the corresponding times were 8 h (range 6–11 h) and 11 h (range 8–16 h), respectively.

In the mepivacaine group, one volunteer was slightly dizzy when mobilized, but the pulse and blood pressure were within normal limits. Four subjects in the bupivacaine group and four in the etidocaine group felt unstable when walking. Two volunteers in the bupivacaine group reported that their heels felt rather "cushiony" and one volunteer in the bupivacaine group had an atactic gait. One volunteer in the etidocaine group had a normal gait but during jogging the right knee felt unstable and he tended to stumble.

Discussion

The duration of analgesia was significantly shorter in the mepivacaine group than in the bupivacaine and etidocaine groups, in accordance with previous reports (11,12). There was a significant difference in the duration of analgesia between the bupivacaine and etidocaine groups in the lowest sacral segments. These results are in agreement with the findings of Scott et al. (13) and Diallo and Nolte (14). Other authors (5,15,16), however, have found that, clinically, the intraoperative sensory blockade provided by etidocaine is less satisfactory than that of 0.5% and 0.75% bupivacaine.

In all groups, hip flexion and knee extension (L1-4) were blocked significantly more rapidly than plantar flexion of the big toe (L5-S2). This may be due to a higher concentration of the local anesthetic agent at the L2-3 region, the site of the epidural injection. The poor degree of motor blockade for plantar flexion of the big toe compared with that for hip flexion and knee extension in the mepivacaine and bupivacaine groups indicates that the lower lumbar and upper sacral segments may be more resistant to local anesthetics (1), which could also explain the "missing analgesic segments" (L5-S2) after administration of bupivacaine in this study.

The duration of maximal motor blockade was significantly longer with etidocaine than with the other two local anesthetics, 5–6 h compared with 1–3 h. Mepivacaine given epidurally provides partial motor blockade and is the only one of the three local anesthetics that is suitable for short-lasting operations on an outpatient, ambulatory basis. Although blockade of the lower lumbar and upper sacral motor segments was slower in onset and not as profound as in the upper lumbar segments, the former did not recover more rapidly during the regression phase than the upper lumbar segments.

During the regression phase, the motor blockade curve seemed to flatten out with increasing duration of the motor blockade, which meant that mepivacaine had the steepest regression curves. In the etidocaine group, 90% of the muscle force returned 10 h, on the average, after epidural injection, an extremely long duration. One of the subjects was mobilized as late as 16 h after the injection. Similar results of long duration with etidocaine have been reported by other authors (16).

In a study by Sinclair and Scott (17), no difference in complete regression of motor and sensory blockades was found after epidural injection of etidocaine, which is in accordance with the present results when the motor blockade was measured with use of the Bromage scale. However, when it was estimated by the quantitative isometric method, the motor blockade was found to recover significantly later than the sensory blockade in the etidocaine group. During onset of the motor blockade, both the Bromage scale and the quantitative method described the relationship between the three local anesthetic groups equally, but the quantitative method gave a more precise differentiation between the three local anesthetics. The Bromage scale was not as sensitive in measuring the degree of motor blockade as was the quantitative isometric method, a finding in agreement with a report by Lanz et al. (7).

During the regression phase when the Bromage scale changed from grade 1 to grade 0, the muscle force of hip flexion and knee extension was <45% of the control value and that of plantar flexion of the big toe was between 40% and 55% in the three groups. Thus, the Bromage scale reflected changes in motor function only in the first half of the regression phase. These results are compatible with those obtained for spinal anesthesia (9,10). After Bromage grade 0 has been reached, subjects given epidural anesthesia should therefore lie recumbent for 1 h (mepivacaine) to 3 h (etidocaine). The subjects were mobilized when the muscle force had reached 90% of the control value, a level that many may consider too high. However, there were subjects who still had a cushiony feeling under the heels on mobilization, had an atactic gait, or felt unstable when walking and jogging. The 90% value therefore seems reasonable.

In conclusion, the spread of sensory blockade was the same for the three local anesthetics tested. In the etidocaine group, the motor blockade was more effective, as expressed by a more rapid onset time, a higher frequency of complete motor blockade, a longer duration of complete motor blockade, and a slower regression phase than those in the bupivacaine and mepivacaine groups. In the etidocaine group, the motor blockade outlasted the sensory blockade. The isometric quantitative method was superior to the Bromage scale in describing the onset, degree, and duration of the motor blockade. Only in the first half of the regression phase did the Bromage scale accurately reflect motor function.

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References

1. Galindo A, Hernandez J, Benavides O, Ortegon de Munoz S Bonica JJ. Quality of spinal extradural anaesthesia: the influence of spinal nerve root diameter. Br J Anaesth 1975;47:41–7
2. Bromage PR. A comparison of bupivacaine and tetracaine i epidural analgesia for surgery. Can Anaesth Soc J 1969;1 37–45.
3. Bromage PR, Datta S, Danford LA. Etidocaine: an evaluation i epidural analgesia for obstetrics. Can Anaesth Soc J 1974;21 535–45.
4. Engberg GH, H:son Holmdahl M, Edström HH. A compariso of the local anesthetic properties of bupivacaine and of ne long-acting agents, HS37 and etidocaine, in epidural analgesia Acta Anaesthesiol Scand 1974;18:277–89.
5. Datton DA, Moir DD, Howie HB, Thornburn J, Watson F Choice of local anesthetic drug for extradural caesarean sec tion. Comparison of 0.5% and 0.75% bupivacaine and 1.5 etidocaine. Br J Anaesth 1984;56:1361–7.
6. Bromage PR. A comparison of the hydrochloride and carbo dioxide salts of lidocaine and prilocaine in epidural analgesia Acta Anaesthesiol Scand 1965;16:55–69.
7. Lanz E, Theiss D, Kellner G, Zimmer M, Staudte H-V. Assess ment of motor blockade during epidural anesthesia. Anest Analg 1983;62:889–93.
8. Axelsson K, Hallgren H, Widman B, Johansson A, Olstrin P-O A new method for measuring motor blockade in the lowe extremities. Acta Anaesthesiol Scand 1985;29:72–8.
9. Axelsson KH, Widman GB, Sundberg AEA, Hallgren S. double-blind study of motor blockade in the lower limbs Studies during spinal anaesthesia with hyperbaric and glu cose-free 0.5% bupivacaine. Br J Anaesth 1985;57:960–70.
10. Axelsson K, Widman GB. Comparison of bupivacaine an tetracaine in spinal anaesthesia with special reference to moto block. Acta Anaesthesiol Scand 1985;29:79–86.
11. Bromage PR, Gertel M. An evaluation of two new loca anaesthetics for major conduction blockade. Can Anaesth So J 1970;17:557–64.
12. Ekblom L, Widman B. A comparison of the properties c LAC-43, prilocaine and mepivacaine in extradural anaesthesia Acta Anaesthesiol Scand 1966;10(Suppl 21):33–43.
13. Scott DB, McClure JH, Giasi RM, Seo J, Covino BG. Effects c concentration of local anaesthetic drugs in extradural block. B J Anaesth 1980;52:1033–7.
14. Diallo B, Nolte H. Zur Frage der Equipotenz von Etidocain un Bupivacain bei der Periduralanaesthesie. Reg Anaesth 198 7:33–8.
15. Koch T, Mathieu K, Lanz E, Theiss D. Periduralanaesthesie m Etidocain. Klinische Untersuchungen zum Einfluss von Va sokonstriktoren auf die sensible und motorische Blockade. Re Anaesth 1984;7:39–43.
16. Lund PC, Cwik JC, Gannon RT. Etidocaine (Duranest^R): clinical and laboratory evaluation. Acta Anaesthesiol Scan 1974;18:176–88.
17. Sinclair CJ, Scott DB. Comparison of bupivacaine and et docaine in extradural blockade. Br J Anaesth 1984;56:147–53.

748 ANESTH ANALG
1989;69:748–51

Delayed Side Effects of Droperidol After Ambulatory General Anesthesia

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The incidence of postoperative effects of droperidol, in the hospital and at home the following night, after general anesthesia for minor outpatient procedures was evaluated in two groups of 50 patients each. Anesthetic techniques were identical except for the presence or absence of 1.25 mg of IV droperidol. There were no differences between the groups with regard to postoperative nausea, vomiting, pain, or time to discharge. In 23% of patients given droperidol, anxiety or restlessness developed after discharge from the ambulatory care unit. No patient not receiving droperidol had these reactions. It is suggested that the routine use of droperidol in all outpatients receiving general anesthesia may not be appropriate.

Key Words: ANESTHESIA, OUTPATIENT. ANESTHETICS, INTRAVENOUS—droperidol.

A great deal of research has been focused on the most appropriate anesthetic techniques for use in ambulatory surgery. The main objective is to define those techniques that allow the most rapid discharge from the surgical facility. Nausea and vomiting, the most common postoperative complications associated with outpatient general anesthesia (1), significantly lengthen time to discharge (2–4). It has been shown that droperidol can prevent postoperative nausea and vomiting in children undergoing strabismus surgery (5,6), and in adults undergoing gynecologic (7) and orthopedic surgery (8). A recent report, however, implicated low-dose droperidol as a cause of extrapyramidal reactions that occurred after discharge from our ambulatory surgical facility (9). We have also found, through routine postoperative phone calls, that many patients from our facility report being anxious or restless the night following surgery. As these seemed to be possible side effects of droperidol, we designed the following study.

Materials and Methods

One hundred consecutive adult women undergoing minor outpatient procedures (dilatation and curettage [D&C], therapeutic abortions [D&E&C], laser cone biopsies of the cervix, and breast biopsy) under general anesthesia were studied. The study was approved by the Hospital Committee on Human Experimentation. Written informed consent was obtained. Patients with a history of psychiatric illness or taking psychotropic drugs were omitted from the study. Also omitted were patients in whom tracheal intubation was deemed necessary. Patients were alternately divided into one of two groups by one of the investigators (B.M.). All patients had an 18- or 20-gauge intravenous (IV) catheter inserted and were monitored by continuous electrocardiogram (ECG) precordial stethoscope pulse oximeter and automated blood pressure cuff. No patient was premedicated. Anesthesia was induced with sufentanil (5 μg IV) and thiopental (5–7 mg/kg IV). Maintenance of anesthesia was with 0%–3% isoflurane and oxygen (5 L/min). Patients breathed spontaneously with manual assistance through an anesthesia face mask using a semiclosed circle system. Group 1 patients received droperidol (1.25 mg IV) immediately before induction of anesthesia. Group 2 patients received 0.5 mL of normal saline solution immediately before induction of anesthesia.

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In the recovery room, patients were evaluated for pain; they were also evaluated every 15 min for nausea and vomiting by a recovery room nurse unaware of the patient study group. If a patient vomited, or spontaneously complained of nausea or pain, this was recorded. Every 15 min each patient was asked, "Are you comfortable?" If the patient said yes, she was not questioned again for 15 more minutes. If the patient replied no, she was asked, "Do you feel sick to your stomach or does something hurt?" Responses to these questions were recorded. Patients requesting pain medication were given 400 mg of oral ibuprofen or 1000 mg of oral acetaminophen. Patients requesting antiemetics were given droperidol (1.25 mg IV) and were excluded from assessment of their status after discharge from the ambulatory care unit. Patients were discharged home when deemed appropriate by an attending anesthesiologist unaware of the patient study group.

Twenty-four to thirty-six hours after discharge, all patients were called on the telephone by a nurse unaware of the study group to which they had been assigned. Along with a list of routine questions, which included questions on postdischarge nausea, vomiting, and pain, patients were asked if they experienced any unusual physical sensations, were unable to sit still, or felt nervous or jumpy the night after surgery. All patients with positive answers were asked to describe their experiences in further detail. If nervous, they were asked if they could think of anything at home that would account for their nervousness. They were also asked if they considered these sensations to be disturbing. If a patient could not be contacted with the initial call, they were called once more later in the day and once the next day.

Continuous variables were compared by unpaired *t*-tests. Discrete variables were compared by using the χ^2-test and confirmed using confidence interval for proportions. A value of $P < 0.05$ was considered statistically significant.

Results

Patients were similar with regard to age, height, weight, and duration of anesthesia (Table 1). There were no differences between the groups in types of surgery performed. Surgical procedures in group 1 included 29 D&Cs, four D&E&Cs, 15 cone biopsies, and two breast biopsies. Surgical procedures in group 2 were 33 D&Cs, three D&E&Cs, 12 cone biopsies, and two breast biopsies. Postoperative data—including time until discharge and nausea, vomiting, or pain before discharge—were also similar (Table 2). The addition of droperidol to the anesthetic technique did not decrease nausea or vomiting before discharge. One patient in each group requested and received an antiemetic in the recovery room. These two patients were excluded from postdischarge data (Tables 3 and 4). Six patients in group 1 and three patients in group 2 could not be contacted by telephone. These patients were also excluded from the postdischarge data. Chi-square analysis of the remaining patients showed that this loss to follow-up did not create a disproportionate number of subjects in either of the experimental groups.

After discharge, two patients in group 1 experienced nausea during the car ride home. One of these patients vomited in the car, and the other after she

Table 1. Patient Height, Weight, Age, and Duration of Anesthetic

	Group 1 (1.25 mg droperidol)	Group 2 (no droperidol)
Number	50	50
Height (cm)	137.2 ± 6.1	137.8 ± 9.3
Weight (kg)	60.0 ± 13.2	64.1 ± 11.4
Age (yr)	36.9 ± 5.3	35.2 ± 8.1
Duration of anesthesia (min)	22.7 ± 12.2	24.3 ± 15.5

Values are mean ± SD.

Table 2. Times to Discharge and Number of Patients with Nausea, Vomiting, or Pain Before Discharge

	Group 1 (1.25 mg droperidol)	Group 2 (no droperidol)
Number	50	50
Time to discharge (min)	129.8 ± 29.4	139.4 ± 38.2
Number of patients with nausea (%)	4 (8%)	7 (14%)
Number of patients with vomiting (%)	1 (2%)	3 (6%)
Number of patients with pain (%)	16 (32%)	16 (32%)

Table 3. Number of Patients with Nausea, Vomiting, or Pain After Discharge

	Group 1 (1.25 mg droperidol)	Group 2 (no droperidol)
Number	43	46
Number of patients with nausea (%)	2 (4.7%)	4 (8.7%)
Number of patients with vomiting (%)	2 (4.7%)	3 (6.5%)
Number of patients with pain (%)	12 (27.9%)	13 (28.3%)

Table 4. Number of Patients with Anxiety, Restlessness, or Unusual Physical Sensations After Discharge

	Group 1 (1.25 mg droperidol)	Group 2 (no droperidol)
Number	43	46
Number of patients with anxiety (%)	10 (23.2%)*	0 (0%)
Number of patients with restlessness (%)	3 (7.8%)	0 (0%)
Number of patients with unusual physical sensations (%)	0 (0%)	0 (0%)
Total number of patients with above conditions (%)	10 (23.2%)*	0 (0%)

*$P < 0.05$.

arrived home. Four patients in group 2 experienced nausea after discharge, one in the car and three after they arrived home. Three of these patients vomited. Twelve patients in group 1 and 13 in group 2 experienced pain after discharge. None of the differences between the two groups was statistically significant.

Ten—that is, 23%—of the patients in group 1 answered yes to the question about unusual physical sensations, restlessness, or nervousness. Of these ten patients, seven said they were nervous and three said they were nervous and couldn't sit still. None said she had any other unusual physical sensations. No patient in group 2 responded yes to this question. No group 1 patient could think of any particular reason for her nervousness, although two suggested it might be the anesthetic. All of these patients found the nervousness or restlessness to be unpleasant.

Discussion

Possible side effects of droperidol include anxiety and extrapyramidal reactions. The extrapyramidal reactions can be classified as parkinsonism, acute dystonia, and akathisia. Ten patients in the present study that were given IV droperidol during induction of general anesthesia reported feeling anxious at home the night after surgery. None could trace this anxiety to any disturbing incident. In addition, three of these patients reported feeling restless. Although this can also be an aspect of nervousness, it is possible that this was a form of akathisia, which can be defined as motor restlessness. Regardless, these occurred only in patients receiving droperidol and were reported by the patients as being unpleasant. None developed serious extrapyramidal symptoms.

When evaluating appropriateness of medications for ambulatory anesthesia, not only adverse reactions that occur in the immediate postoperative period (nausea, vomiting, or drowsiness) and may delay discharge, but also reactions that may occur after the patient is discharged and no longer under direct medical supervision must be considered. Nausea and vomiting after outpatient surgery are probably caused by a combination of patient characteristics, i.e., tendency toward motion sickness, surgical procedures (10), and anesthetic technique (4,11–13). Low-dose droperidol is an effective antiemetic for many (5,6,8) but not all (14) types of surgical procedures. Cohen et al. (14) did not observe any decrease in nausea and vomiting with the use of droperidol in outpatients undergoing therapeutic abortion under general anesthesia without tracheal intubation. Likewise, in the present study, we could discern no antiemetic benefit of droperidol either before or after discharge from the hospital. Our patients also underwent minor gynecologic surgery with mask anesthesia. The anesthetic technique in this study was designed to minimize emetic symptoms and postoperative pain. Nitrous oxide was omitted, as it has been shown to be associated with a higher incidence of nausea and vomiting in outpatients (4). Sufentanil was chosen as the narcotic as it has been found to be associated with less postoperative nausea, vomiting, and pain than fentanyl in outpatient anesthesia (12). Cohen et al. employed fentanyl and 70% nitrous oxide. This may explain the difference in postoperative nausea and vomiting in our studies.

The incidence of nausea and vomiting was similar in both groups both in the recovery room and after discharge from the ambulatory care unit. Intravenous droperidol did not decrease nausea and vomiting at either time. If emetic symptoms were decreased after discharge, this might have outweighed the anxiety or restlessness reported in some of the patients receiving droperidol. This, however, was not the case. Although no patient in this study had what could be considered a serious reaction to droperidol, these can occur after discharge (9). In pediatric patients receiving larger doses of droperidol (0.1–0.17 mg/kg) reactions have been reported to occur as long as 14 h after injection of the drug (15). The incidence and severity of extrapyramidal reactions to droperidol are usually dose-related, and it is likely that if a higher dose of droperidol were used, we would have seen more reactions after discharge. The dose of 1.25 mg used in this study was chosen because the authors believe that this is probably the upper limit of droperidol routinely administered to outpatients.

A total of nine patients, six in group 1 and three in group 2, could not be contacted for postoperative assessment. This loss did not leave a disproportionate number of patients remaining in either group. Patients probably did not answer their postdischarge calls because they were not at home. There is no way of knowing whether or not they experienced postdischarge nausea. If all of the patients without droperidol had emetic symptoms and all receiving droperidol did not, there would be a high, statistically significant difference in postdischarge nausea and vomiting. We believe that this combination is unlikely.

In summary, ten (23%) healthy adult female outpatients undergoing minor surgical procedures under general anesthesia who were given IV droperidol at induction of anesthesia reported feeling unpleasant sensations of anxiety during the day and night after discharge from the surgical facility. In addition, three of these ten patients also complained of restlessness. All ten patients had been given droperidol. No patient not given droperidol had these side effects. It is suggested that for the surgical procedures performed and anesthetic technique used during this study, the use of droperidol as a prophylactic antiemetic is not necessary. This is probably due to the low incidence of nausea and vomiting in the untreated group. As droperidol may only be effective in conjunction with certain anesthetic techniques or surgical procedures and may cause side effects after discharge following ambulatory surgery, it is possible that its routine use in all outpatient anesthetics may not be appropriate.

References

1. Burns K. Postoperative care and review of complications. In: Woo SW, ed. Ambulatory anesthesia care. Boston: Little, Brown, 1982:27–34.
2. Doze VA, Shafer A, White PF. Nausea and vomiting after outpatient anesthesia: effectiveness of droperidol alone and in combination with metaclopramide. Anesth Analg 1987;66:S41.
3. Metter SE, Kitz DS, Young ML, Baldeck AM, Apfelbaum JL, Lecky JH. Nausea and vomiting after outpatient laparoscopy: incidence impact on recovery room stay and cost (abstr). Anesth Analg 1987;66:S116.
4. Melnick BM, Johnson LJ. Effects of eliminating nitrous oxide in outpatient anesthesia. Anesthesiology 1987;67:982–4.
5. Abramowitz MK, Elder PT, Friendly DS, Broughton WL, Epstein BS. Antiemetic effectiveness of intraoperatively administered droperidol in pediatric strabismus outpatient surgery—preliminary report of a controlled study. J Pediatr Ophthamol Strabismus 1981;18:22–7.
6. Lerman J, Eustis S, Smith DR. Effect of droperidol pretreatment on postanesthetic vomiting in children undergoing strabismus surgery. Anesthesiology 1986;65:322–5.
7. Madaj TH, Simpson KH. Comparison of the use of domperidone, droperidol and metaclopramide in prevention of nausea and vomiting following gynecological surgery in day cases. Br J Anaesth 1986;58:879–83.
8. Kortilla K, Kauste A, Auvinen J. Comparison of domperidome, droperidol and metaclopramide in prevention and treatment of nausea and vomiting after balanced general anesthesia. Anesth Analg 1979;58:396–400.
9. Melnick BM. Extrapyramidal reactions to low-dose droperidol. Anesthesiology 1988;69:424–6.
10. Pataky AO, Kitz DS, Andrews RW, Lecky JH. Nausea and vomiting following ambulatory surgery: are all procedures created equal (abstr)? Anesth Analg 1988;67:S163.
11. Rising S, Dodgson MS, Steen PA. Isoflurane v fentanyl for outpatient laparoscopy. Acta Anaesthesiol Scand 1985;29: 251–5.
12. Phitayakorn P, Melnick BM, Vincinie AF. Comparison of continuous sufentanil and fentanyl infusion for outpatient anaesthesia. Can J Anaesth 1987;34:242–5.
13. Lecky JH, Kitz DS, Andrews RW, Young ML, Conaban TJ. Fentanyl vs. isoflurane in outpatient diagnostic laparoscopy: an evaluation of perioperative morbidity and cost. Anesthesiology 1987;67:A433.
14. Cohen SE, Woods WA, Wyne J. Antiemetic efficacy of droperidol and metaclopramide. Anesthesiology 1984;60:67–9.
15. Dupre LJ, Stieglitz P. Extrapyramidal syndromes after premedication with droperidol in children. Br J Anaesth 1980;52:831–3.

ANESTH ANALG
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Interaction Between Nondepolarizing Neuromuscular Blocking Agents and Inhalational Anesthetics

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Although many studies have presented data based on administration of nondepolarizing neuromuscular blocking agents to patients given inhalation anesthesia for 30–45 min, no data exist on the interaction in a clinical situation where the relaxant is administered immediately after the start of anesthesia. We therefore studied the effect of the commonly used inhalation anesthetics, halothane and enflurane, on the clinical pharmacology of atracurium, vecuronium, pipecuronium, and pancuronium. No significant influence of the anesthetic technique on the onset time of the various neuromuscular blocking agents was observed. The duration of action of atracurium, pipecuronium, and pancuronium was significantly prolonged during enflurane anesthesia as compared with the other two anesthetic techniques. The duration of vecuronium blockade was not significantly influenced by enflurane. Halothane, in contrast to enflurane, did not significantly prolong the blockade induced by these agents. The prolongation of atracurium blockade was clinically irrelevant. A fact that is statistically significant but clinically irrelevant is that ***a cumulative effect with atracurium and vecuronium*** *was only seen during enflurane anesthesia and after the fourth maintenance dose. We conclude that there is no clinical indication that the dosage of atracurium and vecuronium during inhalation anesthesia should be reduced, but the doses of pipecuronium and pancuronium should be reduced when prolonged paralysis is not desired.*

Key Words: NEUROMUSCULAR RELAXANTS—atracurium, vecuronium, pancuronium, pipecuronium.

Potentiation in humans of the effects of neuromuscular blocking agents by volatile anesthetics has long been observed (1–5). At equal MAC values, different anesthetics have different potentiating effects (3–5). Most of these studies deal with the evaluation of the intensity of the neuromuscular blockade produced by the neuromuscular blocking agents under the influence of volatile anesthetics. Some investigations also report prolongation of the neuromuscular blockade (2,6). In all these studies the neuromuscular blocking agents were administered 30–45 min after the initiation of ventilation with volatile anesthetics. The more recently developed neuromuscular blocking agents have also been studied according to this same protocol (6,7). Although the methods used in past studies were appropriate for the study of the influence of volatile anesthetics on the action of neuromuscular blocking agents, the situation in daily clinical practice is quite different. In daily clinical practice these agents are usually administered at the beginning of anesthesia, immediately after induction. Consequently, this study was designed to obtain information about the influence of volatile anesthetics on the pharmacologic profile of muscle relaxants when both are used in a clinical situation.

Methods

A total of 350 patients, men and women, between 16 and 65 yr of age, weighing 45–103 kg, ASA physical status I or II, who were scheduled for elective surgery requiring muscle relaxation, gave written informed consent to their participation in this investigation. The study was approved by the Ethics Committees in

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Groningen and Leiden. All patients were free from neuromuscular disease and did not receive any drug that might alter neuromuscular function.

Three anesthetic techniques were used: neurolept, halothane 0.5% and nitrous oxide in oxygen (N_2O/O_2), and enflurane 1% and N_2O/O_2. Diazepam (0.15 mg/kg) was administered orally 60 min before the induction of anesthesia with 4–5 mg/kg of thiopental. After induction a control twitch height was recorded for at least 3 min before the neuromuscular blocking agent was injected. Two times the ED_{95} of each drug (0.1 mg/kg vecuronium, 0.1 mg/kg pipecuronium, 0.1 mg/kg pancuronium, or 0.5 mg/kg atracurium) was used to facilitate endotracheal intubation. Ventilation was with 60% N_2O in O_2 and was adjusted to maintain an end-tidal $F\mathrm{co}_2$ of 0.038–0.042, monitored by a Datascope capnograph. Esophageal temperature was kept above 35.5°C. Fentanyl was administered according to the individual requirements. Halothane (0.5%) or enflurane (1%) was administered directly after induction. The end-tidal concentrations of these volatile agents were measured by a hydrogen flame ionization technique (8,9).

When a given concentration was considered to be insufficient for anesthesia, small-dose intravenous supplements of fentanyl were administered. Neuromuscular function was monitored by single twitches of 0.2-ms duration at a frequency of 0.1 Hz delivered by a Grass S88 nerve stimulator through 22-gauge needle electrodes placed near the ulnar nerve at the wrist. The resulting twitch response of the adductor pollicis muscle was registered with a Statham UC 3 force transducer with a load cell and was recorded on a Datascope recorder. Pipecuronium, pancuronium, and atracurium were each given to 25 patients in combination with one of the three anesthetic techniques. Vecuronium was given to 50 patients during halothane and enflurane and to 25 patients during neurolept anesthesia. In assessing the neuromuscular effects of these four muscle relaxants under the different anesthetic techniques, the following indices were measured: 1) onset time—the time between the end of the injection and maximal depression, which is important in relation to intubation; 2) duration of action—the time between the end of injection and 25% recovery, which is important in relation to surgical relaxation and neuromuscular block reversal (10); and 3) duration of maintenance dose—the time between supplementary injections, which is important as an indicator of the cumulative effect.

A maintenance dose was administered during this study when the twitch height reached 25% of recovery. This bolus dose was always one-quarter of the initial dose.

Table 1. Age of the Patients in the Different Groups

	Anesthetic technique		
Muscle relaxant	Neurolept	Halothane	Enflurane
Atracurium	41 ± 15	39 ± 16	30 ± 11
Vecuronium	36 ± 15	33 ± 12	33 ± 15
Pipecuronium	41 ± 15	36 ± 14	31 ± 11
Pancuronium	38 ± 14	28 ± 10	36 ± 15

Values are mean ± SD, in years.

Table 2. Weight of Patients in the Different Groups

	Anesthetic technique		
Muscle relaxant	Neurolept	Halothane	Enflurane
Atracurium	70 ± 12	75 ± 14	71 ± 12
Vecuronium	74 ± 16	67 ± 11	65 ± 13
Pipecuronium	70 ± 12	76 ± 11	75 ± 9
Pancuronium	73 ± 12	67 ± 13	70 ± 12

Values are mean ± SD, in kilograms.

Table 3. Onset Times

	Anesthetic technique		
Muscle relaxant	Neurolept	Halothane	Enflurane
Atracurium	3.4 ± 1.6	3.0 ± 1.2	2.6 ± 0.6
Vecuronium	2.9 ± 0.9	3.0 ± 0.8	3.3 ± 1.0
Pipecuronium	3.4 ± 1.0	3.2 ± 1.2	3.4 ± 1.0
Pancuronium	3.5 ± 1.6	3.5 ± 1.8	3.6 ± 1.6

Values are mean ± SD, in minutes.

The results were compared with an analysis of variance followed by a multiple comparison according to the method of Scheffe (11); differences were considered significant when $P < 0.05$. Cumulative effects were detected with the Friedman test. Here, too, $P < 0.05$ was considered to be statistically significant.

Results

Physical characteristics of the patients are shown in Tables 1 and 2. Onset times were not significantly influenced by the anesthetic technique (Table 3). In all patients complete abolition of the twitch response was obtained. The duration of the neuromuscular blockade after administration of the bolus dose is shown in Table 4. This table shows that with the exception of vecuronium, a significant increase in the duration of action occurred only during enflurane anesthesia.

Because of the prolonged duration of the pancuronium- or pipecuronium-induced neuromuscular

Table 4. Clinical Duration

	Anesthetic technique		
Muscle relaxant	Neurolept	Halothane	Enflurane
Atracurium	36 ± 9	31 ± 8	44 ± 7[a]
Vecuronium	26 ± 6	28 ± 9	30 ± 9
Pipecuronium	85 ± 31	89 ± 25	125 ± 34[a]
Pancuronium	74 ± 35	90 ± 25	106 ± 35[b]

Values are mean ± SD, in minutes.

[a] Significant prolongation compared with the other two techniques, $P < 0.05$.

[b] Significant prolongation only when compared with neurolept, $P < 0.05$.

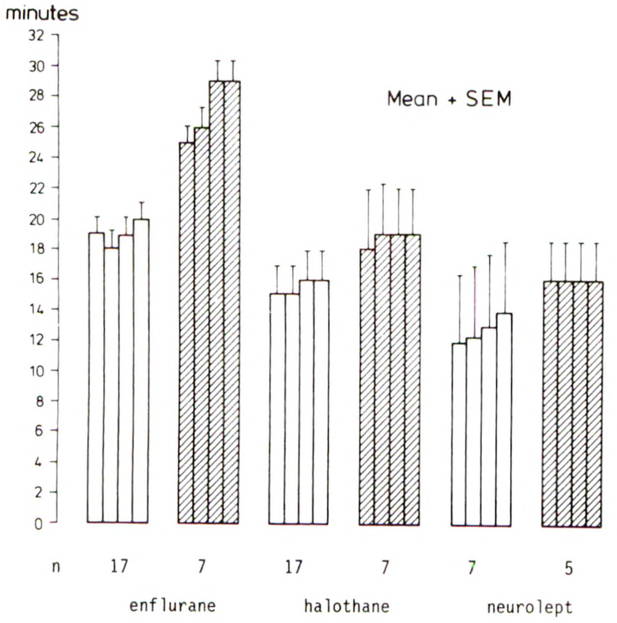

Figure 1. Mean duration of the first four maintenance doses under different anesthetic techniques. □, vecuronium; ▨, atracurium. The four columns represent the four maintenance doses.

blockade and the brevity of the surgery, the duration of the maintenance doses of these agents could not be determined. Figure 1 gives the duration of the first four maintenance doses only for atracurium and vecuronium. A significant prolongation of effect ($P < 0.05$) with the maintenance dose of both drugs (atracurium and vecuronium) was seen only during enflurane anesthesia.

Discussion

The onset time of the four neuromuscular blocking agents studied was not influenced by the anesthetic technique. This could be explained by the slow uptake of inhalational anesthetics by the body. In this investigation the neuromuscular blocking agents were administered 3 min after obtaining a stable control twitch. This means that at the moment of injection of the relaxant, the patient had been exposed to inhalational anesthetics for only about 5 min. Because of the relatively slow uptake of volatile anesthetics by muscle tissue, any potentiating effect (of volatile anesthetics) that may have existed on the action of nondepolarizing neuromuscular blocking agents was likely to become significant only after more prolonged exposure. Muscle tissue equilibrates with the partial pressure of the volatile anesthetic in arterial blood within 1–4 h (12). Most of the interaction studies (1–7) have concerned patients who have been ventilated with the inhalational anesthetics for at least 30–45 min before the relaxant was injected. In daily clinical practice muscle relaxation and tracheal intubation are usually achieved immediately after induction. Consequently, our results more accurately reflect the effect of volatile anesthetics on neuromuscular blocking agents in the daily clinical situation.

The duration of neuromuscular blockade induced by an intubation dose of vecuronium was not influenced by any of the anesthetic technique. Enflurane, however, did prolong the neuromuscular blockades produced by atracurium, pipecuronium, and pancuronium. This finding might be explained by the differences in the duration of effect of the various neuromuscular blocking agents. The duration of a vecuronium-induced neuromuscular blockade during neurolept anesthesia is only 26 ± 6 min. This time-course may be too short for interaction with a volatile anesthetic, as the latter would hardly have equilibrated with the muscle tissue. The increasing duration of the subsequent maintenance doses of vecuronium and atracurium under enflurane anesthesia (significant after the fourth dose, $P < 0.01$) might be an expression of an increasing sensitivity after prolonged exposure to enflurane reflecting a continued uptake of the anesthetic by muscle tissue. Such an increasing sensitivity during prolonged exposure to enflurane has been shown to apply to *d*-tubocurarine (13).

In this study halothane did not prolong the clinical duration of any of the neuromuscular blocking agents, nor was a significant cumulative effect noticed during relaxation with atracurium or vecuronium. The absence of cumulative effect after the use of vecuronium has been reported by many authors (14–18) and by Hughes and Payne (19,20) for atracurium. At equal MAC values, enflurane potentiates the effect of nondepolarizing neuromuscular blocking agents more than halothane does. It can therefore be concluded that although there is no need to reduce the initial dose of vecuronium or atracurium during inhalational anesthesia, it might be necessary during prolonged enflurane anesthesia to reduce maintenance doses. In this study, which had a duration of surgery of up to 200 min, this was not necessary. The duration of pipecuronium and pancuronium blockades is significantly prolonged during enflurane anesthesia, both statistically and clinically. Reduction in the doses of the latter two neuromuscular blocking agents during enflurane anesthesia might be desirable. If this is the case, one should take into account the resultant onset time.

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References

1. Katz RL. Neuromuscular effects of diethyl ether and its interaction with succinylcholine and *d*-tubocurarine. Anesthesiology 1966;27:52–6.
2. Katz RL. Modification of the action of pancuronium by succinylcholine and halothane. Anesthesiology 1971;35:602–6.
3. Miller RD, Eger EI, Way WL, Stevens WC, Donlan WM. Comparative neuromuscular effects of Forane and halothane alone and in combination with *d*-tubocurarine in man. Anesthesiology 1971;35:38–42.
4. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EI. Comparative neuromuscular effects of pancuronium, gallamine and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 1971;35:509–14.
5. Miller RD, Way WL, Donlan WM, Stevens WC, Eger EI. The dependence of pancuronium and *d*-tubocurarine induced neuromuscular blockades on alveolar concentration of halothane and Forane. Anesthesiology 1972;37:573–81.
6. Rupp SM, Miller MD, Gencarelli PJ. Vecuronium induced neuromuscular blockade during enflurane, isoflurane and halothane anesthesia in humans. Anesthesiology 1984; 60:102–5.
7. Stirt JA, Katz RL, Murray AL, Schehl DL, Lee C. Modificatio of atracurium blockade by halothane and by suxamethonium. A review of clinical experience. Br J Anaesth 1983;55:71S–5S.
8. Cramers CA, Trimbos HF. Development of an online analyze for organic anesthetics in inspiratory and end-tidal gasses J Chromatogr 1976;119:71–84.
9. Osinga R, Heuler R. Ein neues Gerät zur kontinuierliche Messung von Narkosendampfen. Prakt Anaesth 1979;14:182–4.
10. Ali HH, Savarese JJ. Monitoring neuromuscular function Anesthesiology 1976;45:216–49.
11. Armitage P, Berry G. Statistical methods. In: Medical research 2nd ed. Oxford: Blackwell Scientific Publications, 1987:200–5.
12. Eger EI. Uptake and distribution of inhaled anesthetics. In Miller RD, ed. Anesthesia. London: Churchill Livingstone, 1981:309–30.
13. Stanski DR, Ham J, Miller RD, Sheiner LB. Time dependen increase in sensitivity to dTc during enflurane anesthesia Anesthesiology 1979;51:S2369.
14. Agoston S, Salt P, Newton D, Bencini A, Boomsma P, Erdmann W. The neuromuscular blocking action of Org NC 45, new pancuronium derivate, in anesthetized patients. A pilo study. Br J Anaesth 1980;52:53S–9S.
15. Crul JF, Booij LHDJ. First clinical experiences with Org NC 45 Br J Anaesth 1980;52:49S–52S.
16. Fahey M, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli PJ. Clinical pharmacology of Org NC 45 (Norcuron). new non-depolarizing muscle relaxant. Anesthesiology 1981 55:6–11.
17. Buzello W, Nöldge G. Repetitive administration of pancuronium and vecuronium (Org NC 45) in patients undergoin longlasting operations. Br J Anaesth 1982;54:1151–7.
18. Mirakhur RK, Ferres CJ, Clark RSJ, Bali IM, Dundee JW Clinical evaluation of Org NC 45. Br J Anaesth 1983;55:119–24
19. Payne JP, Hughes R. Evaluation of atracurium in anaesthetize man. Br J Anaesth 1981;53:45–54.
20. Hughes R, Payne JP. Clinical assessment of atracurium usin the single twitch and tetanic responses of adductor pollici muscles. Br J Anaesth 1983;55:47S–52S.

Fentanyl Inhibits the Canine Carotid Chemoreceptor Reflex

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MAYER N, ZIMPFER M, RABERGER G, BECK A. Fentanyl inhibits the canine carotid chemoreceptor reflex. Anesth Analg 1989;69:756–62.

To investigate the impact of fentanyl on the carotid chemoreceptor reflex, nine mongrel dogs were permanently monitored with electromagnetic flow transducers around the right common iliac artery and with heparin-filled catheters in the descending aorta and in one of the main carotid arteries with the tip just proximal to the carotid sinus. Carotid chemoreceptor activation (CCRA) produced by consecutive injections of nicotine (0.2–0.4 μg/kg) through the carotid catheter elicited bradycardia, expressed as an increase in cardiac cycle length by 140% ± 18%, and a 252% ± 16% increase in mean iliac arterial vascular resistance. These responses were markedly attenuated by fentanyl in a dose-dependent fashion: cardiac cycle length increased only by 50% ± 7% ($P < 0.01$) with 4 μg/kg and by 19% ± 6% ($P < 0.01$) with 8 μg/kg of intravenous fentanyl. These changes were paralleled by significantly ($P < 0.01$) lesser increases in mean iliac arterial resistance (122% ± 9% and 50% ± 5%). It is concluded that fentanyl impairs the integrity of the carotid chemoreceptor reflex.

Key Words: ANALGESICS, FENTANYL—carotid body reflex. RECEPTORS, CHEMO—carotid body.

Since the 1943 classic study of Dripps and Dumke (1), several groups have investigated the impact of anesthetic agents on respiratory control. Whereas earlier studies had revealed either a stimulating or an indifferent effect of anesthetics on peripheral chemoreceptors (2,3), recent investigations have pointed toward an inhibition of the chemoreceptor reflex by anesthetics, thus interfering with the chemical control of respiration (4–6). It is less well documented that the chemoreceptor reflex is not only of importance in the control of respiration but also acts as a powerful cardiovascular reflex within the scope of overall hemodynamic homeostasis (7). It has been shown that halothane (6), enflurane (8), barbiturates (9), and even α-chloralose (9), which has been said to augment or at least maintain reflex responses, impair the cardiovascular component of the chemoreceptor reflex. In comparison to the effects of volatile anesthetics and barbiturates, narcotic analgesics, in particular fentanyl, have fewer effects on the cardiovascular system, provided adequate alveolar gas exchange is maintained by assisted or controlled respiration. Moreover, narcotics are devoid of physiologically significant effects on baroreceptor reflex responses (10). However, the effects of narcotic analgesics on the integrity of the chemoreceptor reflex have not been documented. The objective of the present investigation was therefore to examine the impact of fentanyl on responses elicited by carotid chemoreceptor activation (CCRA) in permanently monitored dogs. The study was confined to observations on changes in cardiac rate and iliac vascular tone, because it is well known that bradycardia and iliac vasoconstriction are prominent after CCRA (8,11). To eliminate not only the antagonistic effects of activation of pulmonary inflation reflexes, but also the complicating influences of respiratory depression induced by fentanyl, experiments were also conducted with ventilation held constant (8–10).

Methods

With approval by the Institutional Animal Care Committee, nine mongrel dogs of either sex weighing

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between 17 and 28 kg were anesthetized with pentobarbital (25–30 mg/kg intravenously [IV]) and permanently implanted with instruments to enable repeated hemodynamic measurements. Through a midline laparotomy electromagnetic flow transducers (Statham, Gould, Inc., Cleveland, Ohio) and hydraulic cuff occluders were implanted around the right common iliac artery and heparin-filled catheters (Tygon) were inserted in the descending aorta and—via a neck incision—in one of the main carotid arteries with the tip just proximal to the carotid sinus, ensuring that the carotid artery remained patent. The instrumentation procedure was associated with only small losses of blood and volume was replaced with Ringer's solution at a rate of 4–6 mL·kg^{-1}·h^{-1}.

Hematocrit values were always within the normal range. All wires and catheters were run subcutaneously and exteriorized between the scapulae. Although strict aseptic procedures were observed at all times, the dogs were given cefamandol (50 mg/kg intramuscularly [IM]) for 3 days postoperatively.

Arterial blood pressure was measured with a strain gauge manometer (Statham P23 Db, Gould, Inc.) connected to the aortic catheter, and iliac blood flow was measured with an electromagnetic flow meter system (model SP 2202, Gould, Inc.). Occlusive zero flow was determined repeatedly throughout the experiments by inflating the hydraulic cuff occluder on the iliac artery. The electromagnetic flow probes were calibrated with timed collections of blood when the animals were killed. Arterial samples from the aortic catheter were collected and analyzed for pH and blood gas tensions (model 168 pH/Blood Gas Analyzer, Corning Medical, Medfield, Mass.).

The experiments were conducted 2–6 wk after surgery when the dogs had completely recovered from operation and had neither arrhythmias nor systemic infections. In the time between the operation and the first experiment the catheters and cables were checked out at least twice and the conscious unsedated dogs were trained to lie on the table and were calmed by a person to whom they were accustomed. On the day of the experiment while the conscious, unsedated animals reclined quietly, continuous records of arterial pressure, iliac flow, and heart rate were obtained. No experiment was started unless heart rate remained within a normal physiologic range during the entire control period and other hemodynamic parameters including arterial pressure and iliac vascular resistance had achieved stable levels.

Carotid chemoreceptor activation was produced by injection of 0.2–0.4 μg/kg nicotine into the carotid catheter, the amount depending on the individual sensitivity to nicotine in each dog. Activation was induced in the unanesthetized, spontaneously breathing dogs before and after slow bolus injection of fentanyl (4 and 8 μg/kg IV), at least 20–40 min apart. In all experiments, the same dose of nicotine was injected in the conscious and anesthetized states. Nicotine was dissolved in 0.9% NaCl; the total injected volume was 2 mL. Although larger dosages of fentanyl are required to produce anesthesia with fentanyl as the sole anesthetic in the dog (12), this dosage was selected as representative of the small amount of fentanyl that can be used in balanced anesthesia and because effects of this dosage of fentanyl on the cardiovascular response to CCRA were observed in pilot experiments. There was no evidence of acute tolerance to fentanyl which was only given when the uniformity of the reflex response was demonstrated by three consecutive injections of nicotine.

Table 1. Experimental Protocol

- Spontaneous ventilation; no fentanyl (n = 3)
  - Carotid chemoreceptor reflex activation (CCRA) produced by 0.2–0.4 μg/kg nicotine into the carotid catheter
  - No other intervention
- Controlled ventilation (succinylcholine infusion, 100 μg·kg^{-1}·min^{-1} IV); (n = 9)
  - CCRA with 0.2–0.4 μg/kg nicotine into the carotid catheter
    - Without fentanyl (n = 7)
    - 10 min after 4 μg/kg (n = 7) and 10 min after 8 μg/kg (n = 7) fentanyl IV
    - Cholinergic blockade (0.15 mg/kg atropine IV) followed by 4 or 8 μg/kg fentanyl IV, and then CCRA 20 and 40 min later, respectively (n = 5)
  - Injection of physiologic NaCl solution instead of nicotine (n = 4)
  - Injection of 10 μg nicotine after ipsilateral dissection of the carotid sinus nerve (n = 4)

As chemoreceptor activity normally fluctuates with respiration (13,14), the injections of nicotine were made at end expiration and repeated at least three times over the subsequent 30 min. Responses to CCRA were also compared in dogs before and after fentanyl (Table 1), but with respiration controlled to eliminate both the complicating influences of respiratory depression and to avoid the antagonistic cardiovascular effects induced by secondary stimulation of pulmonary inflation reflexes (11). To examine the effects of CCRA with ventilation controlled, succinylcholine was infused at a rate of 100 μg·kg^{-1}·min^{-1} IV after an initial dose of 1 mg/kg IV. Ventilation was controlled by a respirator (Engström model ER 300), using a mixture of O_2 and N_2 (FI_{O_2} = 0.3). Minute ventilation was adjusted to maintain arterial pH within the normal range of unanesthetized animals. Arterial Po$_2$ was maintained at levels around 100 mm

Table 2. Arterial Blood Gas Tensions

	Po_2 (mm Hg)	Pco_2 (mm Hg)	pH
Without fentanyl	104.3	33.3	7.41
	±10.0	±1.7	±0.02
Fentanyl (4 μg/kg IV)	106.6	32.9	7.39
	±5.8	±1.7	±0.02
Fentanyl (8 μg/kg IV)	99.8	36.9	7.36
	±4.5	±3.0	±0.03

Values are mean ± SEM.

Arterial blood gas tensions were measured in conscious, ventilated, and paralyzed dogs (without fentanyl) and 10 min after both 4 μg/kg fentanyl and 8 μg/kg fentanyl IV before the respective CCRA.

Hg and arterial Pco_2 at levels below 40 mm Hg (Table 2) to ensure that the chemoreceptors were stimulated only minimally before injection of nicotine.

To eliminate stress associated with tracheal intubation, (a) an ultrashort-acting barbiturate was given to the dogs before intubation (thiamylal, 4 mg/kg IV); (b) 2 mL of a 2% solution of lidocaine was injected into the trachea through the cricothyroid membrane, and (c) the tracheal tubes were coated with a 2% lidocaine ointment. The responses to carotid chemoreceptor reflex stimulation were not tested for 30–60 min after thiamylal was given to exclude most residual effects of this anesthetic. Care was taken not to perform any intervention that would stress the relaxed but conscious animals. In this connection it should be mentioned that the dogs were accustomed to the laboratory personnel as well as to their reclining position. Tachycardia, a prominent feature of the canine response to discomfort, was not observed in the present study. This method has also been used previously in conscious rabbits (15,16) and dogs (8–10).

There is a possibility, however remote, that previous carotid chemoreceptor reflex stimulation by injection of nicotine into the carotid catheter may also have been associated with a reflex response induced by the injection of volume into the carotid catheter or by systemic actions of nicotine itself. However, the injection of neither 2 mL of physiologic NaCl nor nicotine (10 μg) after ipsilateral section of the carotid sinus nerve caused any cardiovascular changes. To eliminate possible confounding influences of simultaneous changes in baseline vascular resistance induced by fentanyl, the responses to CCRA were finally investigated during cholinergic blockade with atropine (0.15 mg/kg IV), with the completeness of the blockade being tested with acetylcholine (40 μg/kg IV).

The data were collected on a multichannel magnetic tape recorder (Analog 7, Philips Electronic Instruments, Inc., Mahwah, N.J.) and recorded on a direct writing oscillograph (model R 612, Beckman Instruments, Inc., Fullerton, Calif.). Mean iliac blood flow and mean arterial pressure were measured using electronic resistance-capacitance filters with 2-s time constants. Mean iliac resistance was calculated as the quotient of mean arterial pressure and mean iliac blood flow. For the purpose of illustration, mean iliac resistance was computed using operational amplifiers configured for a divider circuit. Data for mean iliac blood flow and mean arterial pressure were averaged at the point of the peak increase in mean arterial pressure after CCRA. The bradycardia was evaluated at a higher paper speed comparing the pulse interval for the first beat after carotid chemoreceptor reflex stimulation with the average of eight control beats before stimulation. In that the first beat after carotid chemoreceptor reflex stimulation occurred before the increase in arterial pressure, complicating influences of arterial baroreceptor-mediated bradycardia were avoided.

Average values ± SEM are reported throughout. Responses to CCRA were compared with control using Student's *t*-test for paired comparisons, and baseline values and responses to CCRA after fentanyl were compared with the unanesthetized values using analysis of variance.

Results

Experiments with Spontaneous Ventilation (n = *3*)

Carotid chemoreceptor activation resulted in a mixed biphasic cardiovascular/pulmonary reflex response, i.e., the chemoreceptor and the pulmonary inflation reflex. Whereas the former was characterized by bradycardia, increases in arterial pressure, and iliac resistance, a later phase after the augmented respiratory drive induced by CCRA consisted of tachycardia and a decrease in iliac arterial vascular resistance (Figure 1). These responses were attenuated by fentanyl, i.e., iliac arterial vascular resistance and heart rate increased only trivially when compared with the responses in the unanesthetized states. However, owing to the antagonistic effect of the pulmonary inflation reflex and the complicating influences of the respiratory depression induced by fentanyl, the remainder of the data is from experiments in which ventilation was controlled.

Experiments with Controlled Ventilation

Cardiac cycle length increased 8% ± 6% (mean ± SEM) after 4 μg/kg and 27% ± 13% after 8 μg/kg

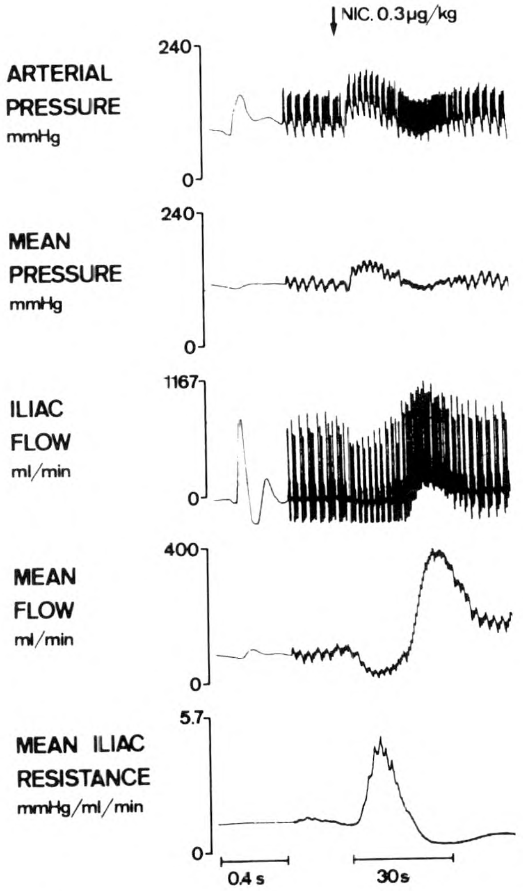

Figure 1. Cardiovascular responses to nicotine-induced CCRA in an animal with spontaneous respiration. Carotid chemoreceptor activation induced a biphasic reflex response. The first phase included an increase in arterial pressure and decreases in heart rate and phasic and mean iliac flow. The second phase, the result of pulmonary stretch receptor stimulation, entails a decrease in arterial pressure and increases in iliac flow and heart rate.

Table 3. Effects of Fentanyl on Responses to Carotid Chemoreceptor Activation

	Cardiac cycle length (ms)		Mean arterial pressure (mm Hg)	
	Control[a]	Change with CCRA (%)	Control[a]	Change with CCRA (%)
Without fentanyl	701	140	104	55
	±22	±18	±2	±8
Fentanyl	756	50	106	35
(4 μg/kg IV)	±23[b]	±7[c]	±4	±5[c]
Fentanyl	887	19	112	25
(8 μg/kg IV)	±46[b]	±6[c]	±3[b]	±5[c]

	Mean iliac arterial flow (ml/min)		Mean iliac vascular resistance (mm Hg·mL^{-1}·min^{-1})	
	Control[a]	Change with CCRA (%)	Control[a]	Change with CCRA (%)
Without fentanyl	115	−55	0.91	252
	±8	±3	±0.07	±16
Fentanyl	100	−38	1.10	122
(4 μg/kg IV)	±8[b]	±4[c]	±0.08[b]	±9[c]
Fentanyl	79	−16	1.42	50
(8 μg/kg IV)	±8[b]	±3[c]	±0.17[b]	±5[c]

CCRA, carotid chemoreceptor activation.
Values are mean ± SEM.
[a] Control represents the values before CCRA.
[b] Control values significantly different: $P < 0.05$.
[c] Change with CCRA significantly different from responses in the absence of fentanyl: $P < 0.05$.

fentanyl; mean iliac arterial resistance increased 21% ± 9% and 56% ± 42% in the absence of CCRA (Table 3).

In measuring the effects of fentanyl on responses to CCRA, the cardiac cycle length of the first beat after CCRA was compared with an average of eight control cycle lengths before CCRA. In animals given fentanyl, CCRA increased cardiac cycle length by 50% ± 7% after 4 μg/kg and 19% ± 6% after 8 μg/kg fentanyl; iliac arterial vascular resistance increased 122% ± 9% and 50% ± 5%, respectively. Thus, responses to CCRA were attenuated by fentanyl in a dose-dependent fashion at a time when pH and arterial blood gas tensions remained constant (Figure 2).

After cholinergic blockade with atropine (0.15 mg/kg), heart rate failed to change significantly with either fentanyl or CCRA; iliac arterial vascular resistance did not increase with fentanyl in the absence of CCRA. When CCRA was performed after 4 and 8 μg/kg fentanyl, iliac arterial vascular resistance (Figure 3) was again attenuated in a dose-dependent manner.

Discussion

Fentanyl, like morphine, exerts no direct depressant effect on cardiac or vascular smooth muscle in concentrations that are associated with analgesic dosages (17,18). In healthy individuals, hemodynamic changes after even large doses of fentanyl are slight. However, even in the presence of unchanged baseline hemodynamics both neural (19) and humoral (20) cardiovascular control mechanisms may be disturbed or even inactivated by various anesthetics. Carotid chemoreceptor activation increases respiratory drive and elicits a complex cardiovascular response mediated by cholinergic and α-adrenergic mechanisms including bradycardia, in our study expressed as an increase in cardiac cycle length, a decrease in coronary vascular resistance (21), and systemic vascular constriction with an increase in arterial pressure.

Whereas earlier studies of the effects of anesthetics on peripheral chemoreceptors dealt primarily with the respiratory aspects of the chemoreceptor reflex (1,4,5), our study focused on the cardiovascular ef-

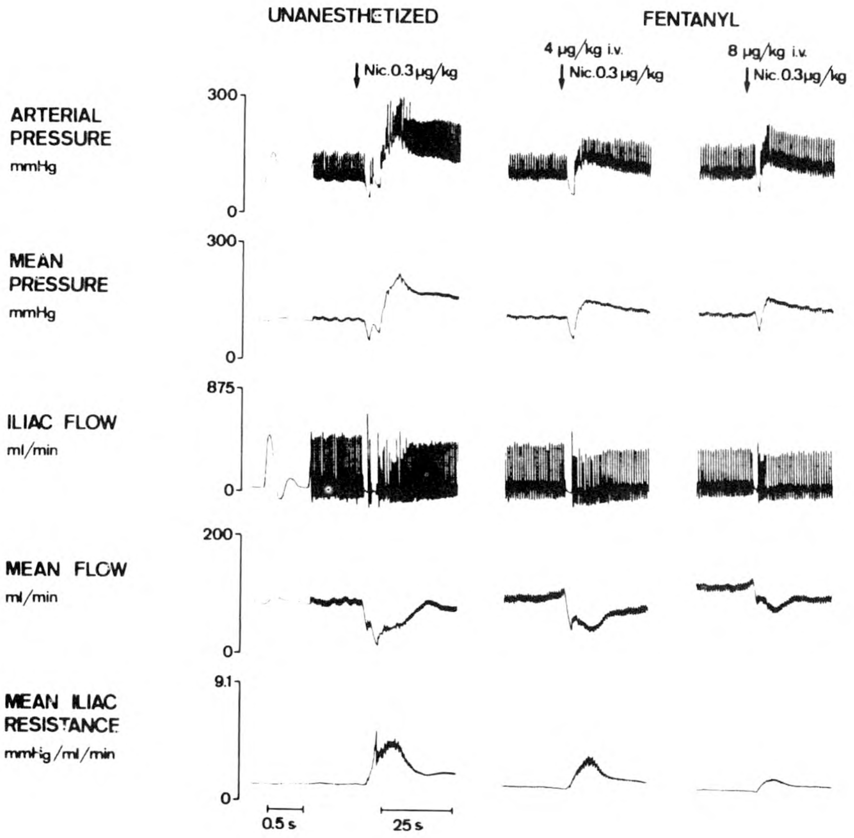

Figure 2. Effects of fentanyl on responses to CCRA. Whereas with controlled respiration the cardiovascular responses to CCRA were devoid of influences of the pulmonary inflation reflex (*left panel*), these responses were depressed by fentanyl (4 and 8 μg/kg IV) in a dose-dependent fashion (*middle* and *right panels*).

fects, as possible interactions with the ventilatory responses are of lesser importance considering the employment of controlled ventilation during general anesthesia. The pronounced attenuation by fentanyl of responses of both the peripheral vasculature and heart rate associated with nicotine-induced CCRA indicates that fentanyl interferes with the chemoreceptor control of the cardiovascular system. These results are in accordance both with those of Zelis et al. (22), who also demonstrated an attenuated arterial constriction after CO_2 challenge under morphine, and with our own previously reported data (10). It is important to note that the pharmacologic stimulation with nicotine did not elicit responses within the central nervous system, inasmuch as no systemic effects were observed after the injection of nicotine and ipsilateral carotid sinus nerve section. Moreover, nicotine is only effective on chemoreceptor and not on baroreceptor efferents (23).

As chemoreceptor stimulation increases respiratory drive causing secondary stimulation of pulmonary inflation reflexes (11,21), and also because of the well-known respiratory depressant effects of narcotic analgesics, effects of fentanyl on the carotid chemoreceptor reflex were compared in this investigation in the anesthetized state with effects obtained on the same day in unanesthetized dogs with ventilation controlled.

In the present investigation, only the responses of the iliac bed and cardiac rate to CCRA were examined. These were selected, as they represent the most dramatic responses to chemoreceptor stimulation (11). It is also important to note that the bradycardia was examined for only the first beat after chemoreceptor stimulation as later beats could well be contaminated by bradycardia mediated through baroreceptor reflexes, because arterial pressure increased after CCRA. In contrast, arterial pressure either remained constant or decreased at the time of the initial cardiac rate response to CCRA. It is recognized that the effects of CCRA on iliac arterial vascular resistance could be modulated by arterial baroreceptor reflexes. However, the arterial baroreceptors would tend to diminish the iliac vasoconstriction most in unanesthetized dogs, but in these dogs the increase in arterial pressure was actually more pronounced. Thus, differences in responses to CCRA in conscious and anesthetized dogs may have even been underestimated in this investigation. Likewise, a direct effect of fentanyl on the arterial baroreceptors is unlikely as fentanyl decreases the afferent receptor drive and thus acts to stabilize the arterial pressure (23).

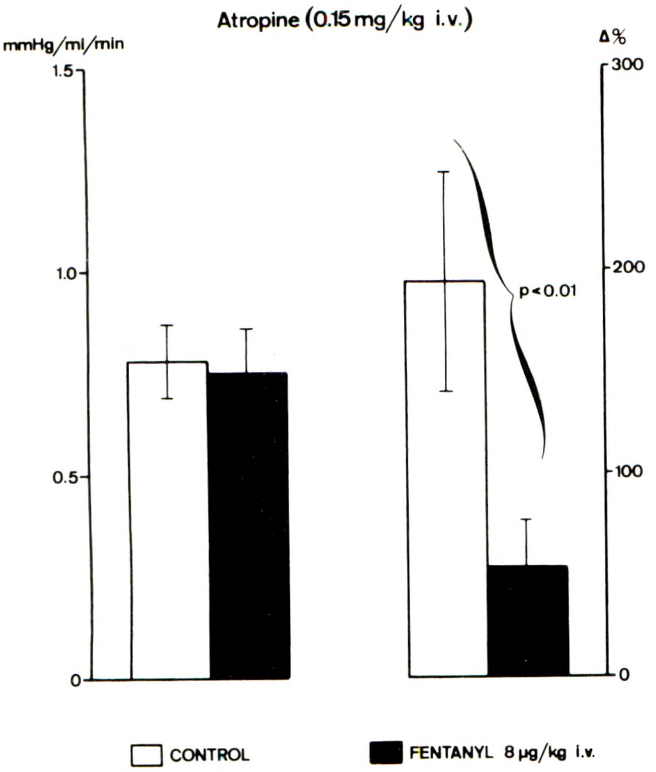

Figure 3. Changes in mean iliac resistance with fentanyl and CCRA after atropine (0.15 mg/kg IV). After cholinergic blockade, fentanyl did not significantly alter baseline values of mean iliac resistance before CCRA (*left*) although the increase in mean iliac resistance after CCRA was still significantly smaller with fentanyl (8 µg/kg IV) when compared with the response in the unanesthetized state (*right*).

Finally, the possibility must be considered that fentanyl-induced bradycardia is associated with a decrease in cardiac output that might initiate secondarily peripheral vasoconstriction. It could therefore be that the failure of iliac arterial resistance to increase with CCRA after the administration of fentanyl could be due, at least in part, to an increase in baseline resistance associated with the administration of fentanyl. For this reason, experiments were repeated on a separate experimental day after cholinergic blockade with atropine. After cholinergic blockade heart rate failed to change significantly with either fentanyl or CCRA. However, as iliac resistance did not increase after fentanyl, the responses to CCRA were considerably depressed. Thus, at least as far as an adrenergic reflex is concerned, the attenuated reflex responsiveness cannot be explained on the basis of different baseline levels.

It should also be emphasized that the impairment of the cardiovascular responses to CCRA with fentanyl were obtained with dosages of fentanyl that do not produce anesthesia in the dog (12). Therefore, if the amount of fentanyl employed were equianesthetic to that in humans, the responses to CCRA might be even more depressed than in humans.

One of the limitations in interpretation of our results involves possible species differences of cardiovascular control principles, including chemoreceptor reflexes. For example, after baroreceptor inactivation control of heart rate is exclusively regulated by the parasympathetic nervous system in the dog but is subject to a mixed vagal-sympathetic influence in humans (24). Another limitation is that cardiovascular diseases might alter reflex excitability (25). In extrapolating our results to the anesthetic care of patients one should bear in mind that the peripheral chemoreceptors are especially important in patients with emphysema or other conditions associated with abnormal gas exchange (26) and that, perhaps, fentanyl, by inhibiting the cardiovascular responses to a hypoxic challenge, might mask clinical signs associated with hypoxemia (27).

In summary, nicotine-induced CCRA resulted in bradycardia and marked increases in iliac vascular resistance in unanesthetized dogs. Both the peripheral vascular and heart rate responses to CCRA were strikingly depressed by fentanyl. Thus, in addition to respiratory depression, fentanyl interferes with the chemoreceptor reflex control of the cardiovascular system.

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References

1. Dripps RD, Dumke PR. The effects of narcotics on the balance between central and chemoreceptor control of respiration. J Pharmacol Exp Ther 1943;77:290–300.
2. Landgren S, Liljestrand G, Zotterman Y. Wirkung von Alkohol, Aceton, Äther und Chloroform auf die Chemoreceptoren des Glomus caroticum. Arch Exp Pathol Pharmakol 1953; 219:185–91.
3. Moyer CA, Beecher HK. Effects of barbiturate anesthesia (Evipal and pentothal sodium) upon the integration of respiratory control mechanisms: a study directed toward improvements of methods for the preclinical evaluation of anesthetic agents. J Clin Invest 1942;21:429–45.
4. Biscoe TJ, Millar RA. Effects of inhalation anaesthetics on carotid body chemoreceptor activity. Br J Anaesth 1968;40:2–12.
5. Duffin J, Triscott A, Whitwam JG. The effect of halothane and thiopentone on ventilatory responses mediated by the peripheral chemoreceptors in man. Br J Anaesth 1976;48:975–81.
6. Davies RO, Edwards MW, Lahiri S. Halothane depresses the response of carotid body chemoreceptors to hypoxia and hypercapnia in the cat. Anesthesiology 1982;57:153–9.
7. Pelletier CL. Circulatory responses to graded stimulation of the carotid chemoreceptors in the dog. Circ Res 1972;31:431–43.

8. Beck A, Zimpfer M, Raberger G. Inhibition of the carotid chemoreceptor reflex by enflurane in chronically instrumented dogs. Naunyn Schmiedebergs Arch Pharmacol 1982;321:145–8.
9. Zimpfer M, Sit SP, Vatner SF. Effects of anesthesia on the canine carotid chemoreceptor reflex. Circ Res 1981;48:400–6.
10. Zimpfer M, Beck A, Mayer N, Raberger G, Steinbereithner K. Einfluss von Morphium auf die Kontrolle des kardiovaskulären Systems durch den Carotis-Sinus Reflex und den Carotis-Chemoreflex. Anaesthesist 1983;32:60–6.
11. Rutherford JD, Vatner SF. Integrated carotid chemoreceptor and pulmonary inflation reflex control of peripheral vasoactivity in conscious dogs. Circ Res 1978;43:200–8.
12. Bailey PL, Port JD, McJames S, Reinersman L, Stanley TH. Is fentanyl an anesthetic in the dog? Anesth Analg 1987;66:542–8.
13. Biscoe TJ, Purves MJ. Observations on the rhythmic variation in the cat carotid body chemoreceptor activity which has the same period as respiration. J Physiol 1967;190:389–412.
14. Fitzgerald RS, Leitner LM, Liaubet MJ. Carotid chemoreceptor response to intermittent or sustained stimulation in the cat. Respir Physiol 1969;6:395–402.
15. Korner PI, Uther JB, White SW. Central nervous integration of the circulatory and respiratory responses to arterial hypoxemia in the rabbit. Circ Res 1969;24:757–76.
16. Korner PI, Shaw J, West MJ, Oliver JR, Hilder RG. Integrative reflex control of heart rate in the rabbit during hypoxia and hyperventilation. Circ Res 1973;33:63–73.
17. Hicks HC, Mowbray AG, Yhap EO. Cardiovascular effects of and catecholamine responses to high dose fentanyl-O_2 for induction of anesthesia in patients with ischemic coronary artery disease. Anesth Analg 1981;60:563–8.
18. Strauer BE. Contractile responses to morphine, piritramide, meperidine and fentanyl: a comparative study of effects on the isolated ventricular myocardium. Anesthesiology 1972;37:304–10.
19. Skovsted P, Price ML, Price HL. The effects of halothane on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. Anesthesiology 1969;31:507–14.
20. Zimpfer M, Kotai E, Mayer N, Placheta P, Steinbereithner K. Einfluss von Morphin auf die Kreislaufkontrolle bei akut progressiver Hämorrhagie. Anaesthesist 1983;32:259–64.
21. Vatner SF, McRitchie RJ. Interaction of the chemoreflex and the pulmonary inflation reflex in the regulation of the coronary circulation in conscious dogs. Circ Res 1975;37:664–73.
22. Zelis R, Flaim SF, Eisele JH. Effects of morphine on reflex arteriolar constriction induced in man by hypercapnia. Clin Pharmacol Ther 1977;22:172–8.
23. Schumacher IG, Arndt JO. Der Effekt von Methohexital, Fentanyl, Dehydrobenzperidol sowie von Chloralose auf die Aktivität der Barorezeptoren des Aortenbogens decerebrierter Katzen. Anaesthesist 1978;27:10–20.
24. Scher AM. Carotid and aortic regulation of arterial blood pressure. Circulation 1977;56:521–8.
25. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. N Engl J Med 1971;285:877–83.
26. Guyton AC. Textbook of medical physiology. 6th ed. Philadelphia: WB Saunders, 1981:516–26.
27. Knill RL, Gelb AW. Peripheral chemoreceptors during anesthesia: are the watchdogs sleeping? Anesthesiology 1982;57:151–2.

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Preoperative Anxiety: Is It a Predictable Entity?

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DOMAR AD, EVERETT LL, KELLER MG. Preoperative anxiety: is it a predictable entity? Anesth Analg 1989;69:763–7.

Most surgical and anesthesia personnel assume that certain factors lead to increased preoperative anxiety, yet the predictability of preoperative anxiety has not been extensively studied. We hypothesized that surgical and anesthesia personnel could be more effective in reducing preoperative anxiety if potential predictors of presurgical anxiety were identified. A sample of 523 patients awaiting elective surgery completed an anxiety scale, had their blood pressure and pulse measured, and had 14 different characteristics recorded. These characteristics included demographics, possibility of cancer, presence of support person, previous surgical experience, and extent of surgery. Female patients were more anxious than male patients, and individuals accompanied by a support person were more anxious than those not accompanied. However, all other factors were noncontributory to anxiety. It appears that patient anxiety does not reflect the assumptions of surgical and anesthesia personnel. This suggests that preoperative anxiety may reflect a patient's personality and coping style more than medical data.

Key Words: PSYCHOLOGIC RESPONSES, ANXIETY.

Most health care professionals are aware that patients experience differing levels of anxiety before invasive medical and surgical procedures. When observing patients anticipating identical surgical procedures, it is not unusual to see these individuals demonstrating wide variations in anxiety. The predictability of preoperative anxiety has not been extensively studied, yet most medical personnel believe that certain patient characteristics serve as red flags. For example, it is widely assumed that patients awaiting cancer surgery are more anxious than patients awaiting a similar procedure for a benign condition. It is also assumed that patients who have had previous surgical experience would be less anxious than patients awaiting their first surgery, as familiarity often reduces anxiety.

Individuals who have contact with patients before surgery, i.e., anesthesiologists, anesthetists, surgeons, and nurses, could be more effective in handling patients' preoperative anxiety if they had knowledge about potential predictors of presurgical anxiety. If one could identify "high risk" patients before these patients actually exhibit increased levels of anxiety, perhaps steps could be taken to prophylactically reduce that anxiety, either through pharmacologic, behavioral, or supportive means.

Despite numerous articles in the anesthesia, surgical, and nursing literature that discuss the identification and treatment of preoperative anxiety, there have been few investigations into the prediction of this anxiety. Although some interventional studies report differing levels of anxiety among different groups of patients, these reports are often anecdotal or not investigated at length. However, there is evidence that some factors can predispose patients to higher levels of preoperative anxiety (1). For example, patients scheduled to have mutilating or symbolically castrating surgery such as mastectomy, hysterectomy, or amputations were found to be significantly more anxious than patients having less emotionally troubling operations (2). In another study, patients having surgery for a malignancy were more anxious than other patients having similar operative procedures (3). In their study of abdominal surgery patients, Chapman and Cox (3) found that patients undergoing renal donor surgery were significantly less anxious preoperatively than kidney recipients or patients undergoing other kinds of abdominal surgery.

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Several studies have also shown that female patients report significantly more anxiety than male (2,4,5). However, one has to take into account that these studies typically compare women undergoing gynecologic surgery with men undergoing abdominal surgery. It is possible that the meaning of the surgery may have affected anxiety ratings rather than just sex alone. Furthermore, the sex differences may simply reflect willingness to admit anxiety as these studies use self-report measures of psychologic states. There is also evidence that age may have an effect on preoperative anxiety; in a study of surgical patients, age was negatively correlated with state anxiety. Younger patients indicated significantly more situational anxiety than did older patients (6). However, it is likely that older patients would have had more experience with surgical procedures than the younger patients. In the same study, education was also negatively correlated with state anxiety. Patients with less education reported significantly more situational anxiety than patients with greater educational levels.

Thus, there is evidence that mutilating or cancer-related surgery can lead to increased anxiety levels. There is also evidence that female patients may be more anxious than male patients, and that patients with less education are more anxious than more highly educated patients. However, there are many more patient characteristics that are known before surgery which might serve as predictors of preoperative anxiety. In this article we will describe a research project aimed at identifying other patient characteristics that may serve to warn health care professionals about the potential for increased preoperative anxiety.

Methods

A total of 523 patients were included in the subject pool. The study was approved by the Committee on Clinical Investigations, Beth Israel Hospital–Harvard Medical School. All patients who were admitted to the Beth Israel Hospital Ambulatory Surgery Division between April 15 and October 1, 1986 were eligible for the study. At Beth Israel, all elective surgery patients who do not need an extensive preoperative workup are admitted on the morning of surgery. The majority of patients come to the hospital ~48 h before surgery for a preoperative visit which includes laboratory testing and visits with an anesthesiologist and an ambulatory surgery nurse. Some patients who are to have local anesthesia for ophthalmologic procedures are not required to have a preoperative visit. Patients who undergo minor surgical procedures are discharged on the same day (surgical day care). Patients who are having major surgery go from the recovery room to their hospital room (same day admit). Thus, the subject pool included patients having minor procedures, such as a dilatation and curettage (D&C), and major surgery, such as cholecystectomy. However, the subject pool did not include patients awaiting more life-threatening procedures such as open-heart surgery patients. These patients are admitted through a different process the day before surgery. All patients were instructed that they were free to not participate in the study. Approximately 5% of the patients chose not to enter the study.

Characteristics that might potentially affect anxiety were chosen based on the literature and on extensive interviews with surgical and anesthesia staff members at Beth Israel Hospital. The following characteristics were chosen: age, sex, religion, nationality, occupation, education, type of surgical procedure planned, whether the surgery was cancer-related or not, presence of a support person preoperatively, whether the patient had come in for a preoperative visit, whether the patient had the same procedure previously, whether the patient ever had surgery before, and whether the patient was a surgical day-care patient or was going to be admitted to the hospital after surgery. The ASA status was not noted, nor was postoperative outcome available, owing to the necessity of numerical coding to ensure confidentiality.

After patients registered at the registration desk in the ambulatory surgery wing, they were given a letter of explanation of the study and a copy of the Spielberger State-Trait Anxiety Inventory (STAI) (7), which they completed while in the waiting room. This inventory is a 40-item, self-report, standardized tool for assessing both acute and chronic levels of anxiety. They were also asked to give their age, sex, occupation, highest level of education, and nationality. When they entered the preoperative preparation area, their primary nurse noted the other potential characteristics listed above, and measured their pulse rate and blood pressure. All patients were assessed before receiving standard preoperative medications.

The Spielberger STAI was scored using raw scores by an individual who was blind to all patient characteristics. All data analyses were performed on the PROPHET system, a national computer resource sponsored by the Division of Research Resources, National Institutes of Health, via a terminal at the Beth Israel Hospital. The data analyses were checked

Table 1. Patient Characteristics

Age: $\bar{x}$ = 39.7 yr
Years of education: $\bar{x}$ = 15.2
Sex: 81% female
Procedures
  57% gynecology
  17% general surgery
  9% urology
  7% plastic surgery
  6% orthopedic surgery
  4% ear-nose-and-throat, dental, and ophthalmologic
Cancer related: 22%
Support person present: 60%
Had preoperative visit: 92%
Had same procedure previously: 23%
Had prior surgery: 85%
Surgical day care: 63%
State anxiety: $\bar{x}$ = 45
Preoperative pulse: $\bar{x}$ = 76 beats/min
Preoperative systolic blood pressure: $\bar{x}$ = 113 mm Hg
Preoperative diastolic blood pressure: $\bar{x}$ = 71 mm Hg

$\bar{x}$ = mean.

twice by two individuals who had no vested interest in the study.

Results

The patient characteristics are reported in Table 1. There were several unexpected results. The mean blood pressure and pulse were lower than expected for a group of patients immediately before surgery; the mean systolic was 113 mm Hg and the mean diastolic was 71 mm Hg. The majority of patients were women (81%) and the most common surgical procedures by far were gynecologic (57%). Three-fifths of the patients had a support person present and 92% of the patients had come in for a preoperative visit. Eighty-five percent of the patients had had previous surgery, a high percentage considering the low mean age of 39.7 yr.

Multiple regressions were run using all patient characteristics to predict each of the dependent variables: anxiety score, pulse rate, and blood pressure. All significance levels reported reflect multiple regression analyses. All r values are partial correlations and reflect the correlation controlling for the other significant independent variables.

The nationality characteristic had to be dropped from the analyses as many patients left this item blank or else misunderstood the question and supplied race instead. Religion was also eliminated because most patients chose not to indicate their religious preference. State and trait anxiety were moderately correlated (r = 0.37, P = 0.0001) so the analysis was performed only on state anxiety as this is presumably a better reflection of current anxiety.

Efficacy of Predictor Characteristics

State anxiety. The multiple regression analysis showed that women had significantly higher anxiety scores than men (r = 0.17, P = 0.003). Patients who had a support person present preoperatively had significantly higher anxiety scores than patients who were alone (r = 0.16, P = 0.006). There was a trend for patients with higher educational levels to be more anxious than patients with less education (r = 0.11, P = 0.066) although this difference was not statistically significant. Patients with cancer had anxiety scores equivalent to those patients having other types of surgery. Patients who came for a preoperative visit had anxiety scores equivalent to those of patients who did not come in for such a visit, although it should be noted that most patients who did not have a preoperative visit were those undergoing ophthalmologic procedures under local anesthesia. Patients having minor surgery (surgical day care) had equivalent anxiety scores to patients having major surgery (same day admit). Patients who had had the same procedure previously had scores equivalent to those of patients who had not. Patients who had had prior surgery had equivalent anxiety scores to patients who had never had surgery. Anxiety did not correlate with the type of surgical procedure; there were no significant differences between any kinds of surgical patients. Age did not correlate with state anxiety, nor did occupation. Thus, having a preoperative visit, having cancer surgery, having major surgery, and having previous experience with surgery had no effect on preoperative state anxiety.

Pulse rate. State anxiety significantly correlated with pulse rate (r = 0.20, $P < 0.001$). Cancer patients had significantly lower heart rates than noncancer patients (r = 0.12, P = 0.048). Patients with high educational levels had significantly lower heart rates than patients with lower educational levels (r = 0.14, P = 0.009). All other predictors of heart rate were not significant.

Blood pressure. Older patients had significantly higher systolic and diastolic blood pressures than younger patients (r = 0.39, $P < 0.0001$). Men had significantly higher blood pressure than women (r = 0.23, $P < 0.0001$ for systolic; r = 0.16, $P < 0.038$ for diastolic). There was a slight trend for patients who had prior surgery to have higher blood pressures than patients who had never had surgery ($r = 0.06$, $P < 0.05$ for systolic; $r = 0.06$, $P < 0.102$ for diastolic). State anxiety did not correlate with either diastolic or systolic blood pressure.

Discussion

Female patients reported significantly more preoperative anxiety than male patients. As the multiple regression analyses controlled for other possible explanatory variables, this difference appears to reflect gender differences. These results are consistent with the literature. It should be noted, however, that the anxiety scores reflect self-reported anxiety levels. Female patients may be more likely than male patients to admit or to report heightened levels of anxiety so that these differences may reflect reporting differences, rather than differences in innate levels of anxiety. Patients who were accompanied by a friend or relative to the preoperative area had significantly higher anxiety levels than patients who were alone. This finding may be explained in two ways. It could be interpreted at face value; the presence of a support person during the preoperative period leads to increased anxiety. This could be caused by forcing the patient to talk with the accompanying person, rather than engaging in distractions such as reading. The alternative and more plausible explanation is that patients who are highly anxious about an upcoming surgical procedure may be more likely to ask a friend or relative to accompany them. Thus, although their anxiety levels are higher than patients who are alone, the levels may actually be lower than if those patients were induced to go unaccompanied. It is important that surgical personnel should not interpret these data to indicate that all friends or relatives should be banned from the preoperative area as it is unclear whether or not they contribute to or lessen anxiety levels. However, the presence of a support person in the preoperative period could serve as a warning that the patient is likely to have increased anxiety levels. It is important to note that despite the presence of statistical significance of both variables, sex and presence of support person, the r values are relatively small (0.17 and 0.16, respectively). Thus, these correlations, although statistically significant, contribute only a modest amount to the variance.

In this study, there was a trend for patients with higher educational levels to express more anxiety than patients with less education. This contradicts the study by Wells et al. (6) which found the opposite. As both studies used the same anxiety scale (Spielberger STAI), the results are rather puzzling. A possible explanation may be that Boston is a more medically oriented city; a significant percentage of our patient population is involved in the medical profession. More highly educated individuals exposed to the media in Boston may be more aware of the risks of surgery and general anesthesia. An alternative explanation is that more educated individuals may be more expressive on self-report assessments of anxiety.

The remainder of the anxiety score results did not support the hypotheses of the surgical and anesthesia staff, nor for the most part did they support the results of other research projects. One of the most unexpected results was that cancer patients did not have higher anxiety levels than noncancer patients. This contradicts previous research (3). It had also been anticipated that gynecologic patients would have higher anxiety levels than patients having other surgical procedures, and that patients having major surgery would be more anxious than patients having minor surgery. Some of these results support the recent work of M. Johnston (personal communication, Royal Free Hospital School of Medicine, London, U.K.). In her study of patients undergoing gynecologic surgery, Johnston found that patients' preoperative worries did not focus as much on the surgery as on the impact on the family and the outcome of the surgery. Thus, preoperative concerns did not focus on the surgical procedure itself. This explanation may account for the lack of differences between different groups of patients as we looked at anxiety in general rather than as it might relate to specific aspects of the experience. Another possible explanation is that we were not specific enough. For example, in a project that compared anxiety in patients undergoing laparoscopy for either sterilization or infertility investigation, there were significant differences in preoperative state anxiety between the two groups (8). Although medical personnel focus on the medical aspects of a surgical experience, patients may have very different concerns.

Although heart rate significantly correlated with state anxiety, which was anticipated, the only significant correlations with predictor variables were contradictory to state anxiety correlations. Patients with higher educational levels had significantly lower heart rates, despite a trend to report higher anxiety scores. Cancer patients had significantly lower heart rates than noncancer patients, although it had been hypothesized that cancer patients would be more anxious than noncancer patients. It is possible that cancer patients may receive more preoperative support and reassurance than noncancer patients. It is also possible that cancer patients practice more denial.

Blood pressure correlations reflected nationally accepted variations rather than influences of predictor variables: older patients had higher pressures than younger patients and men had higher pressures than women, as anticipated. There was a trend for patients who had prior surgery to have higher blood pressures than patients who never had surgery. However, in a population of 523 patients, *P* values of 0.05 (systolic) to 0.102 (diastolic) are usually not clinically significant.

It had been anticipated that there would be a number of patient characteristics that could be utilized in a preoperative setting to predict patient anxiety. The aim of this study was to alert surgical and anesthesia staff members to patients who were likely to be highly anxious before surgery so that steps could be taken before that point in time to decrease anxiety. This study has shown that female patients do express more anxiety before surgery than male patients and that the presence of a supportive person in the preoperative area can serve as a warning of heightened anxiety levels.

However, the most important information presented here is that patient anxiety does not reflect the assumptions of medical personnel. It would seem obvious, for example, that a patient facing major surgery would be more anxious than a patient facing minor surgery but this is apparently not the case. It is likely that medical staff are more sympathetic to patients facing major surgery; it is equally likely that one may become annoyed at a patient experiencing extreme anxiety before minor surgery. The assumptions that medical professionals themselves represent concerning factors contributing to anxiety have not been supported. However, this study was limited by the utilization of self-report measures. These levels may not actually reflect true anxiety levels, but rather the willingness to express anxiety. The potential limitations of the study include the use of a self-report measure of anxiety and the exclusion of patients admitted the day before surgery. Future research might include more projective tests of anxiety as well as a population facing life-threatening surgery.

Most individuals who deal with surgical patients have preconceived notions about factors that predispose patients to be highly anxious. This project investigated 11 of these factors and found all but two noncontributory. Thus, the main conclusion of this project is that preoperative anxiety may reflect more of a patient's personality and coping style, rather than the concrete facts presented in a patient's medical chart. Surgical and anesthesia personnel could be more prepared to help reduce preoperative anxiety if an individual approach is used, rather than relying on preconceived assumptions.

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References

1. Domar A, Noe J, Benson H. The preoperative use of the relaxation response with ambulatory surgery patients. J Human Stress 1987;13:101–7.
2. Graham L, Conley E. Evaluation of anxiety and fear in adult surgical patients. Nurs Res 1971;20:113–22.
3. Chapman C, Cox G. Determination of anxiety in elective surgery patients. In: Spielberger C, Sarason IG, eds. Stress and anxiety. Washington, DC: Hemisphere, 1977.
4. Mathews A, Ridgeway V. Personality and surgical recovery: a review. Br J Clin Psychol 1981;20:243–60.
5. Wolfer J, Davis C. Assessment of surgical patients' preoperative emotional condition and postoperative welfare. Nurs Res 1970, 19:402–14.
6. Wells J, Howard G, Nowlin W, Vargas M. Presurgical anxiety and postsurgical pain and adjustment: effects of a stress inoculation procedure. J Consult Clin Psychol 1986;54:831–5.
7. Spielberger C. Manual for the state trait anxiety inventory STAI (form Y). Palo Alto, Calif: Consulting Psychologists Press, 1983.
8. Wallace L. Psychological adjustment to and recovery from laparoscopic sterilization and infertility investigation. J Psychosom Res 1985;29:507–18.

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Orientation of Fibers in Human Dorsal Lumbar Dura Mater in Relation to Lumbar Puncture

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FINK BR, WALKER S. Orientation of fibers in human dorsal lumbar dura mater in relation to lumbar puncture. Anesth Analg 1989;69:768–72.

Longitudinal insertion of a lumbar puncture needle bevel is less likely to cause post–lumbar puncture headache than is transverse insertion. The reason for this has not been entirely clear. We investigated the direction of dural fibers in posterior L3-4 dura mater obtained from three autopsies and tallied it in three orthogonal planes. Under low-power light microscopy the tissue appeared to be composed of lamellae branching irregularly and directed concentrically to the spinal cord. Electron micrographs (×5000) revealed that the lamellae consisted mainly of bundles of collagen fibers that pursued wavy courses in various directions. The lamellae also contained branching elastic fibers, many of which were directed longitudinally. This arrangement of fibers probably minimizes the tendency of a dural puncture hole to gape under tension if the needle bevel is directed longitudinally.

Key Words: ANATOMY, DURA MATER. ANESTHETIC TECHNIQUES, SPINAL.

The incidence of post–spinal puncture headache is markedly reduced by the use of small-bore needles for lumbar puncture (1). Franksson and Gordh (2) showed that small-bore needles decreased the number of dural fibers broken by the needle point and thus diminished the leak of cerebrospinal fluid (CSF) through the puncture. They noted that fewer fibers were broken when the plane of the bevel was longitudinal during introduction than when it was transverse. However, this observation was necessarily made on excised dura mater; such dura mater is not subject to the longitudinal stresses and circumferential (or "hoop") stresses imposed on the sac of dura mater by the CSF in vivo. In the microphotographs of Franksson and Gordh (2), the longitudinal perforations were lenticular and the transverse ones nearly circular, but measurement now reveals that the cross-sectional areas were virtually identical and suggests that the *shape* of the hole may also be a factor in the incidence of headache (3). More recently, observers of the spinal dura mater by scanning electron microscopy have classified it as a loose connective tissue (4), but the arrangement of the collagen and elastic fibers in this tissue remains undescribed. At present, headache after lumbar puncture is uncommon except in parturient women (5), but some aspects of its occurrence are still not yet fully understood. For example, the reasons for its relatively high incidence in middle-aged and lower incidence in older and younger patients are uncertain (5,6). This article contributes an analysis of the fibrous structure of lumbar dura mater and discusses the implications of the findings in understanding the factors involved in post–lumbar puncture headache.

Methods

Light Microscopy

The specimen consisted of an L-3 nerve root cuff and attached anterior and posterior dura mater from a man of 43 yr who died of acute respiratory distress syndrome. It was removed by one of the investigators (Dr. Fink) at autopsy, fixed in formalin, dehydrated, and embedded in paraffin. Sections 5 μm thick were cut in three orthogonal planes (transverse, radial longitudinal, and tangential longitudinal, as in the insets of Figure 2) and stained with hematoxylin and eosin or by van Gieson's method (which stains collagen red, cytoplasm yellow, and nuclei black). Microphotographs (Figure 1) were calibrated with a 20-μm grating.

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Electron Microscopy

A piece of posterior L3-4 dura mater shaped to indicate its orientation was removed by the investigator at autopsies on two adults aged 74 and 43 yr who had died of cardiovascular and respiratory disease and a 14-yr-old youth who died of a pineal tumor. The specimens were fixed in Zamboni's paraformaldehyde-picric acid, stained with uranyl acetate and lead citrate, and embedded in Epon. Sections were cut in the transverse, radial longitudinal, and tangential longitudinal planes ("tangential" here refers to a grazing plane, as distinguished from the meaning used by Hatfalvi [7] for a longitudinal bevel inserted in the midline and directed laterally at an angle of 30–40° to puncture the dura mater) and mounted on electron microscopic (EM) grids. An assistant photographed an entire, randomly selected EM grid square (~0.088 × 0.088 mm) at ×2000, prepared and assembled enlarged prints (to ×5000) in a montage, placed and oriented a square lattice on the montage, and marked the lattice position but concealed the orientation. The naïve investigator scored the direction of the collagen fibers in 121 evenly spaced 6-mm squares of the 25 × 25-cm lattice, sampling a total of ~7% of the area enclosed. The dominant direction of the dural collagen fibers in each of the 6-mm squares was scored (see Table 1, top half) according to whether it was predominantly vertical (V), horizontal (H), or anteroposterior (AP) relative to the top and bottom of the square. Also listed in the top half of Table 1 are empty squares (O), interpreted as having been occupied by the amorphous ground substance of the matrix (the extracellular matrix is the major part of connective tissue and is composed of fibers embedded in ground substance). Not listed are the elastic fibers, which made up the balance of the 726 squares (two sections per plane per specimen, three specimens) surveyed in each of the orthogonal planes.

Because of their great width, small number, and straight courses (8), the elastic fibers were surveyed and scored separately in the whole of a 25 × 25-cm grid graduated in 0.8 cm covering 88% of the region surveyed for collagen. Each quarter of each 0.8-cm square was scored, for a total of 1600 quarter-squares per section, or a total of 9600 in the six sections in each plane (Table 1, bottom half). Quarter-squares judged to be more than half-filled with elastic fiber were scored as 1, those less than half-filled were scored as 0.

To compare directional incidences among the collagen or elastic fibers, the individual section counts included in the three entries for the same orientation (the orientations identified at the foot of Table 1) were summed ($n = 18$) and the statistical significance of differences were evaluated by Student's two-ended t-test.

Results

Light Microscopy

In transverse and radial longitudinal sections, the dura mater appeared to be composed of multiple, irregularly branching lamellae arranged concentrically relative to the spinal cord (Figure 1). The clefts between the lamellae were occupied by the connective tissue ground substance. (As indicated above, connective tissue is composed of cells and extracellular matrix made by fibroblasts, the matrix in turn being composed of fibers and ground substance.) Regions posterior and anterior to the spinal cord were structurally indistinguishable. Individual collagen or elastic fibers were not recognizable by light microscopy in these preparations. The term "fibers" when used to describe the appearance of dura mater in the light microscope (2) refers to the composite lamellae or strands.

Electron Microscopy

Collagen fibrils typically ~0.06 μm in diameter were the dominant element (Figure 2), arranged in wavy, irregularly interlacing bundles trending in various directions. Sparser, densely staining elastic fibers and gaps devoid of structure (representing ground substance) occurred at irregular intervals. The elastic fibers were notable for their large diameter, typically 1–2 μm (8), their dark amorphous content packed with long parallel fibrils, and a rectilinear course generally either longitudinal or transverse but occasionally branching. The direction of the elastic fibers was consistent in both sections of each plane, between all three planes of sectioning, and between all three specimens.

The results of the survey of fiber directionality in each of the planes are summarized in Table 1. Column headings V, H, and AP indicate directions relative to the lattice grid. The corresponding orthogonal directions in the specimens are given at the foot of the columns. The summed longitudinal and circumferential directionality scores, evaluated by the t-test, did not differ significantly either for the collagen or the elastic fibers ($P > 0.1$) but were significantly larger than the corresponding radial scores ($P < 0.005$). The scarcity of radial directionality may

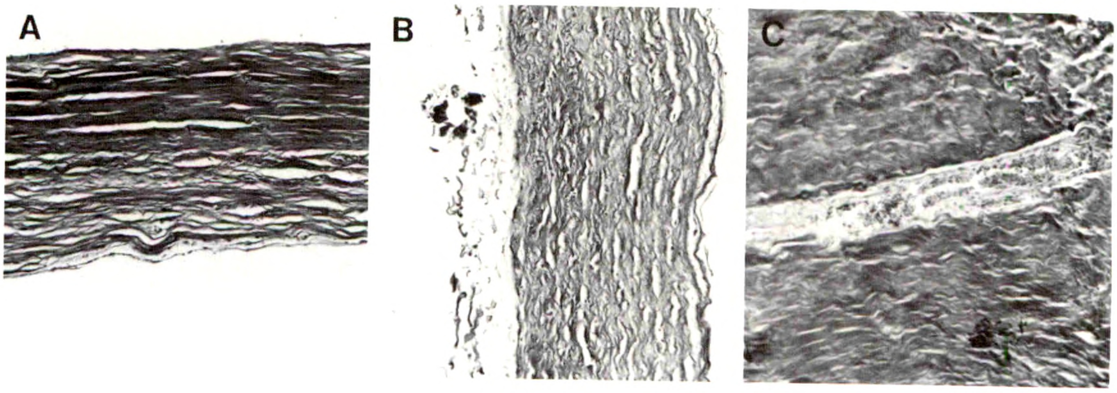

Figure 1. Orthogonal sections of posterior L-3 dura mater from a subject aged 43 yr. (**A**) Transverse; (**B**) radial longitudinal; (**C**) tangential longitudinal; van Gieson stain. **C** is from near the epidural surface; the cranial direction is toward the top. In **B** the epidural surface is on the left; in **A** it is at the top. The tightly lamellated appearance near the epidural surface is typical. The general direction of the lamellae and strands in **A** and **B** is concentric and consistent with the appearance in **C**, where the general direction of the strands is clearly transverse. ×30.

in part simply be due to radially directed portions of fibers primarily coursing longitudinally or circumferentially. A very low total, 12, of radial collagen scores in the subject aged 74 yr was the only hint of age-related difference.

Discussion

Viewed in the light microscope (Figure 1), the dura mater presents a compact structure composed of concentric irregularly branching lamellae enclosing clefts that are referable to ground substance. The abundance of the interlamellar ground substance may well account for the ready passage of drugs through the dura mater (4,9).

In electron micrographs (Figure 2), the lamellae are seen to be composed principally of interlacing bundles of collagen fibers that apparently do not take a strongly marked longitudinal direction, in contrast to the larger and sparser elastic fibers that consistently course in one of two directions: directly longitudinal or directly transverse. If dural fiber directionality responds to the mechanical stresses in the dura mater, one might expect it to have a predominantly transverse (horizontal) tendency because the cerebral and spinal dural mater enclose a space that is quasicylindrical in its spinal portion. An increase in CSF pressure, such as in coughing, would be expected to produce an increase in spinal dural stress at least twice as great in the transverse circumferential direction (hoop stress) as in the longitudinal direction (10), but the scores in this survey give no indication that dural collagen fiber directionality is adjusted to the difference in the magnitude of these stresses. The scores are, however, consistent with the impression gained from naked eye inspection of the micrograph montages that different collagen fiber bundles often run at approximately right angles to each other. In sharp contrast to the wavy course and ill-defined directionality of the collagen bundles is the marked rectilinearity of the elastic fibers. The rough equality of the numbers running transversely and longitudinally should be noted; however, the sections examined represent only a very small portion of the parent tissue and manifest great variability within the sampled area. Paradoxically, the numbers imply inequality of elastic resistance to hoop and longitudinal stress. There is no excess of transverse elastic fiber to withstand the excess hoop stress and this means that an increase in CSF pressure will tend to stretch the trellis of elastic fibers concentrically rather than longitudinally. At such times the nerve roots will tend to be drawn laterally at the points where they exit from the dural sac. Thus the obliquely outward and downward course of the roots between the spinal cord and dura mater seems arranged to absorb such movement with a minimum of longitudinal stress and strain on the nerve fibers. The envelope of CSF and cuff of dura mater through which the segmental roots exit from the spinal dural sac probably serve the same mechanics.

The excess increase in hoop stress during increases in CSF pressure should tend to make the edges of a hole created by a longitudinally oriented needle bevel gape more than those created by a transverse one, and tests on an immobile cylindrical model support this idea (11) but clinical observation does not (12,13). There is, however, evidence that flexion of the vertebral column increases the longitudinal tension in the spinal cord and meninges in situ (14); this effect could cause the edges of a cut by a transversely directed

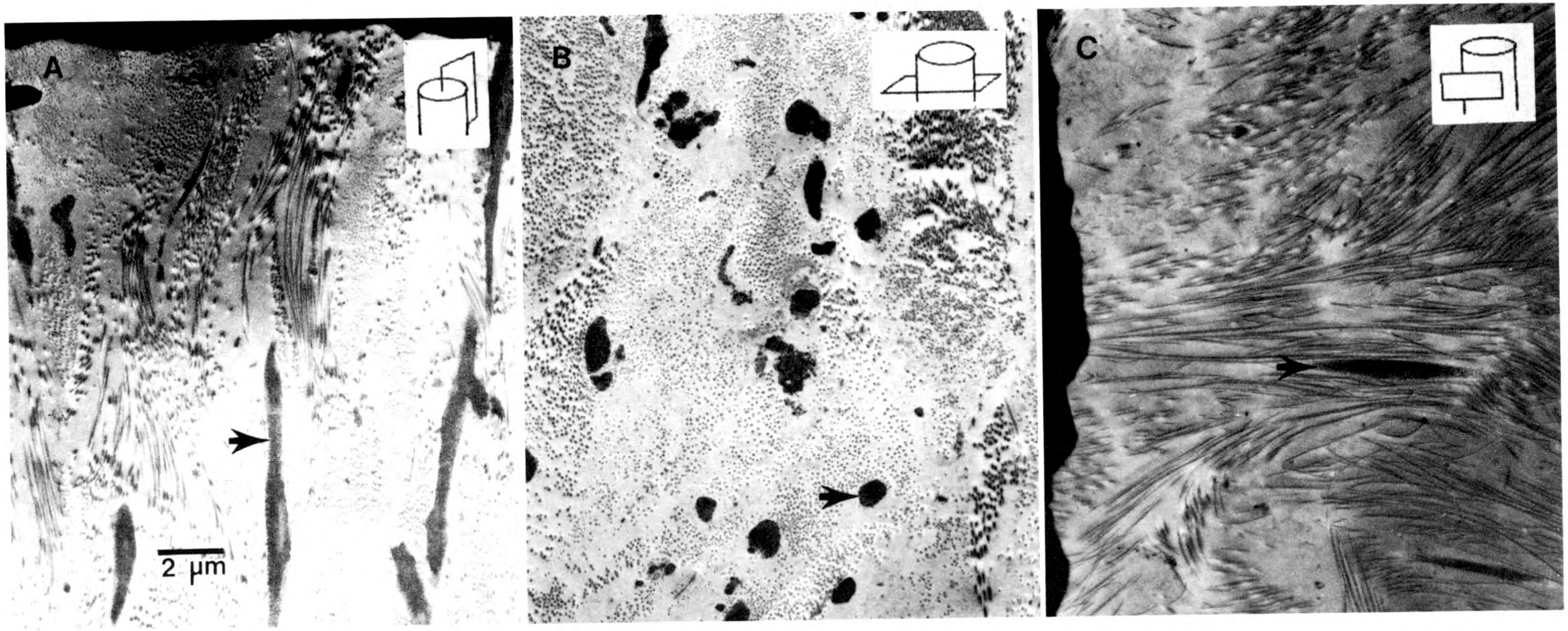

Figure 2. Electron micrographs of posterior lumbar dura mater from the same subject as in Figure 1. (**A**) Radial longitudinal; (**B**) transverse; (**C**) tangential longitudinal. Thickness of sections, 1 μm. Photographed at ×2000, enlarged to ×5000; scale bar, 2 μm. In **A** and **C** the cranial direction is toward the top; in **B** the epidural side is toward the top. Black areas at the margins are parts of the supporting grid. The collagen fibers typically occur in bundles that follow a wavy course evident in **C** and appear punctate in cross section, as in **B**. The elastic fibers (*arrowheads*) are 1–2 μm wide, stain darkly, and follow a straight course, mainly either transverse or longitudinal. The arrangement of the collagen was very variable. The direction of the elastic fibers was consistent in all sections and planes.

Table 1. Counts of Grid Squares Occupied by Fibers Directed Vertically (V), Horizontally (H), and Anterioposteriorly (AP) or by Ground Substance (O)

	Plane of section											
	Radial longitudinal				Transverse				Tangential longitudinal			
Orientation on grid	V	H	AP	O	V	H	AP	O	V	H	AP	O
Collagen												
Total squares	178	36	307	172	92	23	418	157	116	210	136	248
Mean	29.7	6.0	51.2	28.7	15.3	3.8	69.7	26.2	19.3	35.0	22.7	41.3
SE	7.6	2.9	6.3	10.8	4.3	2.3	5.3	2.1	4.1	7.7	6.8	5.8
Surveyed area (%)	24.5	5.0	42.3	23.7	12.7	3.2	57.6	21.6	16.0	28.9	18.7	34.2
Elastic fibers												
Total quarter-squares	569	84	60		355	26	244		100	219	14	
Mean	94.8	14	10		59.2	4.3	40.7		16.7	36.5	2.3	
SE	22.5	6.5	2.4		15.0	3.0	15.9		7.8	14.4	1.0	
Surveyed area (%)	79.8	11.8	8.4		56.8	4.2	39.0		30	65.8	4.2	
Orientation in body	Long	Rad	Circ		Circ	Rad	Long		Long	Circ	Long	

Long, longitudinal; Rad, radial; Circ, circumferential. Collagen was surveyed in 726 squares; 121 squares per section—two sections per plane and per specimen (three specimens); elastic fibers were surveyed in quarter-squares of 600 squares.

needle bevel to gape more than those of a longitudinally directed one, and would cause a correspondingly greater leakage of CSF from the transversely directed one and a greater liability to post–spinal puncture headache.

References

1. Shnider SM, Levinson G. Anesthesia for obstetrics: current concepts. 2nd ed. Baltimore: Williams & Wilkins, 1987:175.
2. Franksson CV, Gordh T. Headache after spinal anesthesia and a technique for lessening its frequency. Acta Chir Scand 1946;94:443–54.
3. Ready LB, Woodland RV, Haschke RH. Spinal needle affects rate of fluid leak across human dura (abstr). Anesthesiology 1985;63:A241.
4. Sato J, Sato H, Yamamoto T, Yokokawa K, Hiraga K, Mizuguchi T. The mechanism of dural permeability to narcotics and local anesthetics. Jpn J Anesthesiol 1985;35:917–27.
5. Abouleish E. Pain control in obstetrics. Philadelphia: JB Lippincott, 1977:123.
6. Vandam LD, Dripps RD. Long-term follow-up of patients who received 10,098 spinal anesthetics: syndrome of decreased intracranial pressure headache and ocular and auditory difficulties. JAMA 1956;161:586–91.
7. Hatfalvi BJ. The dynamics of post-spinal headache. Headache 1977;17:64–6.
8. Rhodin J, Dalhamn T. Electron microscopy of collagen and elastin in lamina propria of the tracheal mucosa of rat. Exp Cell Res 1955;9:371–5.
9. Moore RA, Bullingham ES, McQuay HJ, et al. Dural permeability to narcotics: in vitro determination and application to extradural administration. Br J Anaesth 1982;54:1117–28.
10. Gordon JE. Structures or why things don't fall down. New York: Penguin Books, 1983:119–23.
11. Fink BR. Orientation of spinal needle bevel: effect on fluid leak in a model. Reg Anesth 1987;12:45–6.
12. Mihic DN. Post-spinal headache and relationship of needle level to longitudinal dural fibers. Reg Anesth 1985;10:76–81.
13. Norris MC, Leighton BL, DeSimone CA. Needle bevel direction and headache after inadvertent dural puncture. Anesthesiology 1989;70:729–31.
14. Smith CG. Changes in length and position of the segments of the spinal cord with changes in posture in the monkey. Radiology 1956;66:259–65.

Efficacy of Oral Cyclosporine Given Prior to Liver Transplantation

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BROWN MR, BRAJTBORD D, JOHNSON DW, RAMSAY MAE, PAULSEN AW. Efficacy of oral cyclosporine given prior to liver transplantation. Anesth Analg 1989;69:773–5.

The bioavailability of oral cyclosporine (CYS) dissolved in a large quantity of milk given just before liver transplantation (LTX) was evaluated in 30 patients, given randomly timed oral CYS before LTX, by measurements of CYS blood levels at induction, 2 h later, and at the time of graft reperfusion. Adequate blood CYS levels, defined as ≥500 ng/mL (FPIA), could reliably be achieved only when the drug was administered 4 to 7 h preoperatively. Patients receiving the drug <4 h preoperatively generally had low levels thereafter (two of seven patients had ≥500 ng/mL in any sample, compared with 13 of 14 patients in the 4–7-h group, P < 0.011); an interval of >7 h yielded unpredictable results. Fluids and blood products transfused, and preoperative ascites or ICU care, were not related to blood CYS levels. Oral CYS should be given 4 to 7 h before LTX to achieve adequate levels.

Key Words: SURGERY, TRANSPLANTATION—liver. LIVER, TRANSPLANTATION—cyclosporine. IMMUNE RESPONSES, SUPPRESSION—cyclosporine.

Cyclosporine (CYS) is a mainstay of immunotherapy for solid organ transplantation. It is frequently given in a single oral preoperative dose before liver transplantation, with the intention of providing a therapeutic blood level at the time of graft reperfusion. While the pharmacokinetics of chronic oral CYS therapy have been well described (1–3), it has not been determined whether a randomly timed preoperative dose results in desired blood levels. The importance of this question is enhanced by the fact that this drug must be dissolved in a substantial amount (≥180 mL) of chocolate milk, and may be administered just before surgery, thus possibly increasing the risk of aspiration. The present study relates time of preoperative CYS administration with levels attained during anesthesia and surgery.

Methods

Following approval of the Institutional Review Board, informed consent was obtained from 30 patients admitted for initial orthotopic liver transplantation. No patient had received cyclosporine previously. Patients with severely impaired renal function (oliguria or GFR < 40 mL/min) did not receive CYS preoperatively and thus were excluded.

Patients were given CYS 10 mg/kg mixed in 180 mL chocolate milk orally shortly after hospital arrival, 2 to 10 h preoperatively. Premedication consisted of either oral diazepam 5 to 10 mg or IM midazolam 4 to 8 mg; no patient received metoclopramide, sucralfate, or H_2 blocking agents. After induction of anesthesia with thiopental or ketamine, followed by succinylcholine and sufentanil for tracheal intubation, the first blood sample was drawn for CYS levels (whole blood fluorescence polarization immunoassay [FPIA] TDx, Abbott Labs, Chicago, Ill.). Anesthesia was maintained with sufentanil, pancuronium, and isoflurane in air/oxygen. A second blood sample for CYS assay was drawn 2 h after induction, and a third within 15 min following reperfusion of the grafted liver. Nasogastric tubes were placed, but not suctioned. Fluid and blood-product administration was recorded for each time interval. Veno-venous bypass was employed in all cases. Urine output remained

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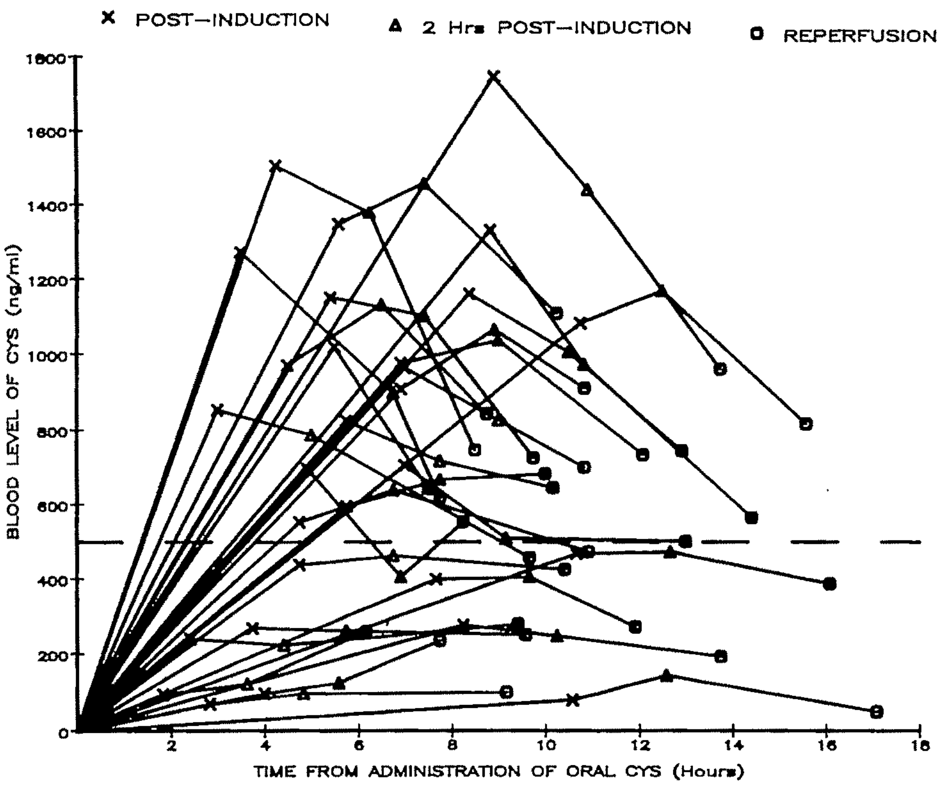

Figure 1. Cyclosporine (CYS) blood levels in 30 patients measured following induction of anesthesia, 2 h later, and 15 min after graft reperfusion. The therapeutic level is considered to be 500 mg/mL (*dashed line*).

adequate in all patients. Patients were given intravenous CYS within the first 24 h postoperatively and thereafter based on adequacy of renal function in accordance with the immunosuppressive protocol at this institution.

Multiple regression analysis was performed to determine if a relationship existed between CYS blood levels and either times of CYS administration or volumes and times of fluid and blood-product administration. Nonparametric methods were used to test whether the presence of ascites or preoperative intensive care unit stay affected the drug levels. Significance between groups in contingency tables was computed with χ^2 tests using Yates' corrections.

Results

Cyclosporine blood levels are shown graphically in Figure 1. The data in Table 1 indicate that administration of CYS less than 4 h before anesthetic induction generally yielded blood levels less than 500 ng/mL at the time of graft reperfusion. Patients given CYS more than 7 h before induction of anesthesia had widely variable and unpredictable levels. The minimum blood level considered therapeutic in our institution is 500 ng/mL.

Patients had received a cumulative volume of 448 ± 75 mL (mean ± SD) of crystalloid but no blood products at the time of induction; 1990 ± 154 mL and 490 ± 123 mL, respectively, 2 h after induction; and 3814 ± 268 mL and 2347 ± 511 mL at the time of graft reperfusion. No significant linear relationships could be established between fluids or blood products administered and changes in CYS levels, even when data were normalized for weight and body surface area.

The decreases in CYS blood levels between 2 h after induction and the time of graft reperfusion were significantly correlated (R = 0.90, $P < 0.001$) with the absolute drug levels and the length of time between the measurements. The CYS blood levels were directly related to the absolute drug levels, and were inversely related to the time intervals between measurements.

Table 1. Cyclosporine Blood Levels as a Function of Time Between Oral Administration and Anesthetic Induction

	Time between CYS dose and induction		
Patients with	<4 h	4 to 7 h	>7 h
CYS levels > 500 ng/mL at any measurement	2/7	13/14[a]	4/8
CYS levels > 500 ng/mL at reperfusion	1/7	12/14[b]	4/8

CYS = cyclosporine.
[a]$P < 0.011$, [b]$P < 0.007$ compared to 0- to 4-h recipients.

Whether or not the patients were in the intensive care unit preoperatively, or had significant ascites, did not affect CYS blood levels. No episodes of regurgitation or aspiration occurred.

Discussion

Although CYS is normally described as reaching peak blood concentrations 2 to 4 h after an oral dose (1), adequate levels (i.e., CYS > 500 ng/mL) were not seen in our patients unless more time had elapsed before anesthesia—ideally, 4 to 7 h.

Many factors are, in all probability, involved in the results of this study. Preoperative anxiety, intraabdominal pathology, or debilitation related to preexisting diseases might have delayed gastric emptying or absorption, contributing to diminished CYS blood levels at the time of induction of anesthesia. There is also normally a wide variability between individuals in the rate of absorption of oral CYS, even in healthy, nonanesthetized subjects (3). Furthermore, CYS blood concentrations increase dramatically following biliary T-tube clamping in liver transplant recipients, indicating that CYS intestinal absorption is dependent upon enterohepatic circulation (4), which would be highly unpredictable in the patients in the present study.

Therapeutically inadequate CYS blood levels 2 h after induction and at the time of reperfusion may be related to the effects of anesthesia and of major upper abdominal surgery, including delayed gastric emptying. Isoflurane anesthesia significantly reduces the absorption of orally administered CYS in rats, even in the absence of surgery (5).

Although large alterations in blood volume and fluid replacement may be seen during liver transplantation, in the present study there was no significant correlation between fluid or blood administration and CYS blood levels. However, analysis of the relationship of the second and third CYS samples to the time interval between those samples and the absolute drug levels revealed a high correlation. This suggests first-order rate kinetics for redistribution and elimination of the drug.

The definition of therapeutic CYS blood levels varies between institutions and assays; notably, the FPIA assay used here yields values that are approximately 80% of those given by whole-blood RIA assays in use elsewhere, and our results should be interpreted with this in mind. Further, there is no general agreement as to optimal levels of CYS at the time of transplantation; each major institution has developed its own target for maintenance of CYS blood levels, controlled comparisons of which are lacking.

We conclude that there is no clinical justification for the administration of oral CYS immediately before liver transplantation, and submit that the potential risks (e.g., vomiting and aspiration) are thus unjustified. Cyclosporine should be given orally no less than 4 and no more than 7 h preoperatively in order to achieve optimum blood levels.

References

1. Newburger J, Kahan BD. Cyclosporine pharmacokinetics in man. Transplant Proc 1983;4(Suppl 1):197–8.
2. Alexander DP, Horning L, Bowers LD. Cyclosporine metabolite disposition after oral administration in pretransplant end-stage renal disease patients. Transplant Proc 1988;20(Suppl 2):499–508.
3. Grevel J. Significance of cyclosporine pharmacokinetics. Transplant Proc 1988;20(Suppl 2):428–34.
4. Tredger JM, Naoumov NV, Steward CM, et al. Influence of biliary T-tube clamping on cyclosporine pharmacokinetics in liver transplant recipients. Transplant Proc 1988;20(Suppl 2):512–5.
5. Gelb AW, Freeman DJ, Robertson KM, Zhang C. Isoflurane alters the absorption kinetics of cyclosporine (abstract). Anesth Analg 1989;68:S98.

Serum Ammonia Levels in Response to Glycine Infusion in Normal and Cirrhotic Rats

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FRINK EJ Jr, DIGIOVANNI DA, DAVIS JR, BROWN BR Jr. Serum ammonia levels in response to glycine infusion in normal and cirrhotic rats. Anesth Analg 1989;69:776–82.

Elevated serum ammonia may play a role in central nervous system derangement after transurethral resection of the prostate. Glycine used as a surgical irrigant for prostate resection produces ammonia as a by-product after liver and renal metabolism. The presence of liver dysfunction often leads to an inability to remove generated ammonia from the circulation. To determine whether the presence of cirrhosis allows significant metabolism of glycine and the resulting serum ammonia levels generated, the production of ammonia after glycine infusion was examined in normal and cirrhotic rats. Hepatic microsomal enzyme induction was produced in male Sprague-Dawley rats given sodium phenobarbital, added to the drinking water to hasten the development of cirrhosis, by increasing the toxicity of carbon tetrachloride given intragastrically to one group at weekly intervals for production of cirrhosis. A control group was maintained under similar conditions except for carbon tetrachloride dosing. The end point for production of cirrhosis was the development of ascites. Two weeks after the development of ascites in the cirrhotic rats and the discontinuation of phenobarbital in both groups, both control and cirrhotic rats were anesthetized with IP pentobarbital and glycine (1.25 g/kg; 7.5%) was given intravenously. Venous blood samples were taken at intervals up to 120 min for serum ammonia analyis. After the final serum ammonia sample, lethal pentobarbital injection was given and livers and kidneys removed for histologic analysis.

Terminal body weight, glycine dose, and renal histology were not different between groups. Liver weights were greater in cirrhotic rats. Baseline serum ammonia levels were also greater in the cirrhotic rats. After glycine infusion, cirrhotic rats developed higher peak serum ammonia levels that remained elevated longer than those in control animals. Results suggest that during glycine administration in cirrhotic rats the ability to metabolically convert glycine to ammonia is not substantially impaired. Metabolism by the liver of circulating ammonia, however, appears to be significantly decreased. It is concluded that the presence of cirrhosis leads to more elevated and prolonged serum ammonia levels after glycine infusion in cirrhotic as compared with noncirrhotic rats.

Key Words: SURGERY, UROLOGIC—transurethral prostatectomy. LIVER, CIRRHOSIS—glycine and ammonia metabolism. METABOLISM—glycine; ammonia.

The intravascular absorption of irrigating solution during transurethral resection of the prostate (TURP) may be associated with several clinical sequelae. Cardiorespiratory compromise and central nervous system derangement may occur due to intravascular volume overload and electrolyte imbalance. Changes in mental status are generally believed to be associated with dilutional hyponatremia and reduced serum osmolality. There are several reports (1,2) of patients who developed postoperative encephalopathy in association with elevated serum ammonia levels and with use of glycine as the surgical irrigant during resection. Glycine solutions are often used as the irrigant for this procedure (3), and its oxidative deamination results in the production of ammonia.

Liver disease and congenital or acquired defects in the urea cycle often cause inability to metabolize ammonia with resultant increase in its serum level. It has been suggested that the presence of liver disease may lead to an increased risk of hyperammonemic encephalopathy with glycine absorption after TURP (2). On the other hand, although the liver normally

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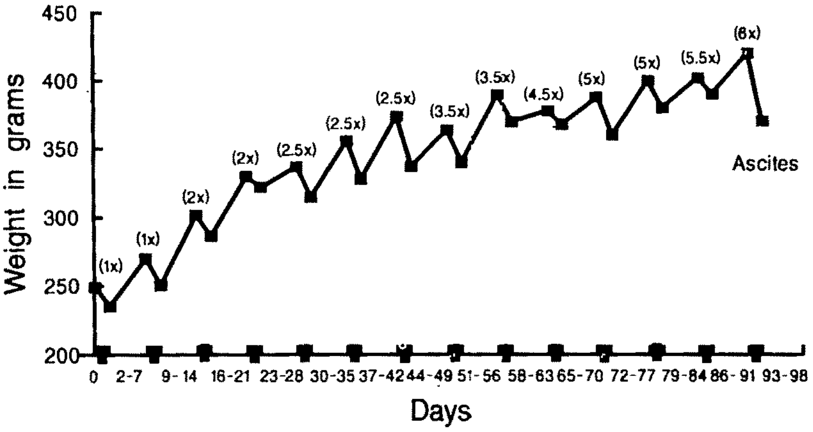

Figure 1. Representative example of body weight changes during CCl_4 administration to produce cirrhosis. Dosing was weekly with subsequent CCl_4 dosage based on maximal weight loss 2 days after the previous dose. The initial dose (1x) was 0.04 mL CCl_4 with the remaining volume in corn oil to a total of 0.5 mL. Subsequently, the dose of CCl_4 was increased (as a multiple of x) without a change in the total volume of 0.5 mL.

contributes to metabolic removal of ammonia from the blood, the liver also contributes to the production of ammonia through metabolism of glycine. The effect of liver dysfunction on the production of ammonia during TURP with use of glycine as the irrigant has, however, not been studied. Although it is well established that the cirrhotic condition leads to a poor ability to handle ammonia, it is unclear whether cirrhosis so impairs hepatic metabolism as to prevent significant production of ammonia from administered glycine. Therefore, we used a model of cirrhosis in the rat to evaluate how the presence of liver disease may affect the metabolism of glycine, production and metabolism of ammonia, and the resultant serum ammonia levels.

Methods

With the approval of the animal care committee of the University of Arizona, 25 male Sprague-Dawley rats (Harlan) were used in the experimental procedure. All rats were housed in hanging cages and allowed a standard diet ad libitum. After a 1-wk quarantine, 15 of the rats were assigned to a group for generation of cirrhosis. The additional 10 animals were used as a control (noncirrhotic) group.

Induction of Cirrhosis

Phenobarbital (0.05% vol/vol) was added to the drinking water of both groups to produce hepatic biotransformation enzyme induction and hasten the production of cirrhosis in the rats in which cirrhosis was to be generated. Administration was continued until development of ascites. The control animals were handled similarly with regard to phenobarbital dosing. One week later, carbon tetrachloride (CCl_4) dosing was begun on a once weekly basis. CCl_4 (0.04 mL) (in corn oil [0.5-mL total volume]) was given intragastrically using a 5 F, 40-cm infant feeding tube (Argyle) based on a method described by Proctor and Chatamra (4). The nasogastric tube was inserted into the stomach after 5 min of 2.5% isoflurane anesthesia to lightly sedate the animal. The initial starting dose was 0.04 mL of CCl_4 in 5 mL of corn oil in each animal. Subsequent increases or decreases in the CCl_4 weekly dosage were based on the animal's response to the previous dose. The animal's weight loss 2 days after the previous dose was used to determine if the subsequent dose should be increased, decreased, or remain the same (Figure 1). If the animal lost significant (>5%) body weight 2 days after a dose, the subsequent dose was decreased by 0.02 or 0.04 mL of CCl_4 per 0.5 mL of total volume (CCl_4 + corn oil). An increase in dose was given if the animal maintained its weight or showed a weight gain. No change in the dosage occurred if the animal showed a modest weight loss (<5% body weight). This method allowed the controlled induction of disease with little mortality compared with fixed dosage regimens that do not account for individual animal response. The end point for production of cirrhosis was the development of ascites that was most visible with the animals in the supine position while lightly anesthetized with isoflurane. After the production of cirrhosis, a 2-wk period without phenobarbital or CCl_4 dosing was allowed for stabilization before experimental testing.

Glycine Administration

The control and cirrhotic animals were anesthetized with pentobarbital (65 mg/kg IP) for insertion of a femoral venous catheter. The catheter was flushed with heparinized saline solution (50 U/mL) after each

Table 1. Total Glycine Dose Administered and Terminal Body/Organ Weights

Group	Glycine dose (mg)	Weights (g)		
		Body	Liver	Kidney
Control (n = 10)	523.6 ± 17.8	418.9 ± 14.3	16.8 ± 0.1	3.73 ± 0.04
Cirrhotic (n = 10)	520.3 ± 15.5	416.2 ± 12.4	22.2 ± 0.3[a]	3.74 ± 0.03

Data shown as mean ± SEM
[a] Differs from control group, $P < 0.05$.

blood sample removal. After the removal of a 500-μL blood sample for determination of baseline ammonia levels, glycine 1.25 g/kg (7.5% wt/vol in 0.9N sodium chloride) was administered via the femoral catheter over 5 min. Subsequent blood samples were obtained via the femoral vein 15, 30, 60, 90, and 120 min after completion of the glycine infusion. Blood samples were centrifuged at 6000 *g* for 10 min and the plasma was frozen at −70°C for subsequent analysis. Serum ammonia levels were determined spectrophotometrically (Sigma, St Louis, Mo.) with use of a Beckman spectrophotometer.

After the final blood sample was obtained, the liver and kidneys were removed for subsequent weighing and histologic analysis after lethal pentobarbital injection. Liver and kidney histologic sections obtained from each animal in both groups were stained with hematoxylin and eosin for histologic analysis. Liver samples obtained from cirrhotic animals were graded on level of cirrhosis and hepatocellular changes and classified as mild, moderate, or severe cirrhosis (5).

Statistical analysis for comparison between control and cirrhotic animals used paired *t*-tests. One-way analysis of variance (ANOVA) was used to evaluate significance of ammonia changes with respect to individual animals and time. Statistical significance was defined as $P < 0.05$.

Results

Of the 15 animals undergoing induction of cirrhosis, the first ten developing ascites were used for the analysis of ammonia response to glycine infusion. (Only one animal of the original 15 died during early CCl_4 dosing.) The average time for production of cirrhosis was 13 wk, but the time interval ranged from as early as 8 to as late as 17 wk.

Mean body weight and subsequent glycine dose did not differ between control and cirrhotic groups (Table 1). Liver weights were significantly greater in cirrhotic rats than in control rats, but kidney weights did not differ. All rats in the cirrhotic group had ascites present at postmortem laparotomy.

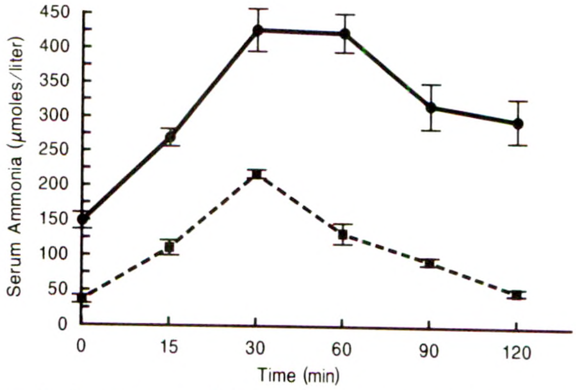

Figure 2. Serum ammonia levels after glycine infusion in control (■) and cirrhotic (●) animals. Values represent mean ± SEM with n = 10.

Changes occurred in serum ammonia levels during the 120-min evaluation period in both control and cirrhotic rats. There was no difference in ammonia levels noted between animals within each group, indicating group homogeneity with respect to serum ammonia changes. Baseline ammonia levels were higher in cirrhotic than in control rats ($P < 0.05$). Peak serum ammonia levels (427.64 ± 31.05 μmol/L) were also significantly greater in cirrhotic than in control rats (217.69 ± 6.17 μmol/L) (Figure 2). Analysis of absolute value change in ammonia level from baseline showed that, at each time interval, values in the cirrhotic group were greater than control values. In cirrhotic rats, serum ammonia levels remained elevated at 120 min, whereas levels in control rats had by this time point returned nearly to baseline values. Serum ammonia level peaked in 9 of 10 control animals by 30 min and by 60 min in one animal, whereas in the cirrhotic animals, peak serum levels were attained at 30 min in six animals, 60 min in three animals, and 90 min in one animal. Histologic examination showed the presence of nodular cirrhosis in all cirrhotic animals (Figure 3). None of the livers in control rats showed evidence of hepatocellular disease. Based on histologic criteria (5), cirrhosis in two livers was classified as mild, in four as moderate, and in four as severe cirrhotic with hepatocellular changes. Histologic examination of the kidneys showed no abnormality other than occasional periph-

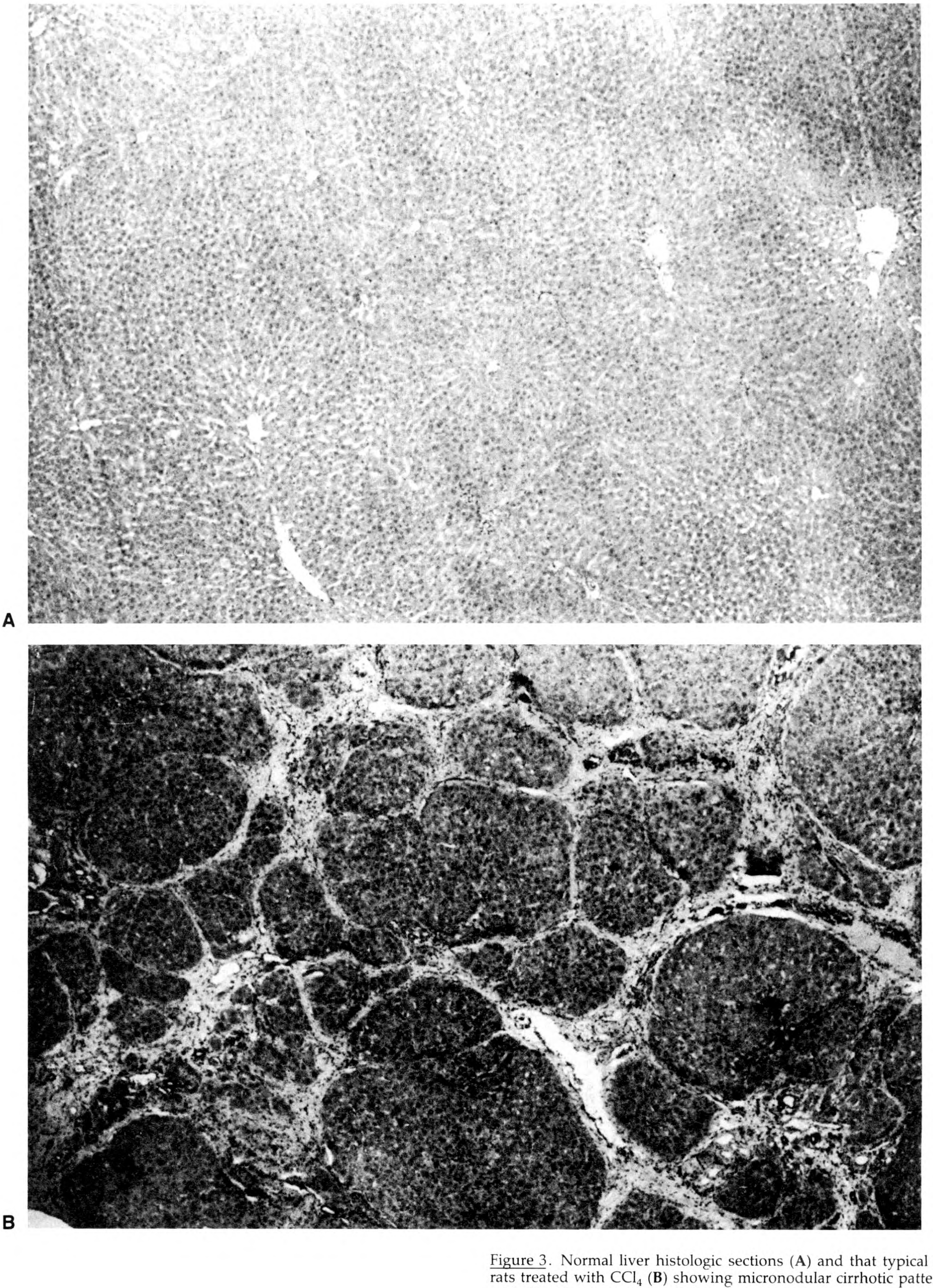

Figure 3. Normal liver histologic sections (**A**) and that typical of rats treated with CCl_4 (**B**) showing micronodular cirrhotic pattern with fibrosis and hepatocellular changes.

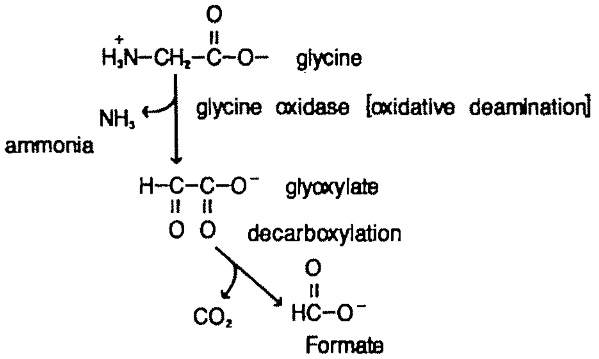

Figure 4. The metabolic pathway for the conversion of glycine to ammonia in the liver and kidney.

eral focal glomerulosclerosis consistent with changes attributable to animal age in both groups of rats.

Discussion

The results obtained in this study show that serum ammonia levels are significantly greater in cirrhotic than in control rats after glycine IV infusion. The cirrhotic animals began with higher serum ammonia levels and, after glycine infusion, the absolute increase in ammonia level was greater than that in control animals at all time points studied.

The "TURP syndrome," which occasionally occurs after prostate resection, may consist of adverse hemodynamic changes as well as central nervous system (CNS) derangement. The CNS alterations that result have generally been ascribed to hyponatremia and hypoosmolality (6,7). Recent evidence suggests, however, that the mental or visual disturbances, or both, may be more complex than simple hyponatremia.

Glycine (1.5% wt/vol) is often used as a surgical irrigant for TURP. Glycine itself functions as an inhibitory neurotransmitter in the CNS and retina (8–10), and increased blood and, presumably, CNS levels may be responsible for mental and visual disturbances associated with the TURP syndrome in some cases.

Glycine is normally metabolized in the liver and kidney by oxidative deamination to produce ammonia (Figure 4). Elevations in serum ammonia level after TURP may contribute to or cause CNS abnormalities associated with the TURP syndrome (1,2). Elevated blood ammonia concentrations in humans cause mental dysfunction. In patients with liver disease, elevated serum ammonia levels are believed to be one of the etiologic factors in hepatic encephalopathy. The central effects of ammonia may be mediated by increasing CNS levels of the inhibitory neurotransmitter serotonin and/or by decreasing the production of the excitatory neurotransmitters norepinephrine and dopamine (11).

Although all three previously discussed factors (elevated glycine, hyponatremia, and hyperammonemia) may play a role in encephalopathy after prostate resection with use of glycine as the irrigant, it is likely that each may in some instances be more important in particular patients. There seems to be good evidence that, at least in some patients, elevated serum ammonia levels after glycine absorption lead to mental status changes in the absence of significant decrease in serum sodium levels (1,2). Elevated serum glycine levels are likely not a factor in some patients because symptoms of mental dysfunction often are noted as serum ammonia levels are increasing, by which time serum glycine levels have already decreased. Several authors (1,2) have questioned whether the patient with liver disease might be at increased risk for hyperammonemia after TURP with glycine. Hoekstra et al. (2) found that one patient in their series developed CNS changes 3 h postoperatively. This patient had a serum ammonia level of 428 μmol/L (normal 11–70 μmol/L) with a serum sodium level of 130 mEq/L and was the only patient in their study with preoperative liver dysfunction. It appears that certain patients (perhaps, as implied by results of this study, those with liver dysfunction) may develop perioperative mental derangement based on elevated serum ammonia levels after TURP with use of glycine irrigant.

The glycine infusion dosage in our study was based on animal weight. Although there was variability in animal weight within each group, there was no difference in glycine dosage between groups. So that glycine administration could be accomplished without circulatory overload, 7.5% wt/vol glycine was used rather than 1.5% wt/vol. A dose of 1.25 g/kg was chosen because, in normal dogs, a glycine dose of 1 g/kg resulted in a serum ammonia level >100 μmol/L, a level that might be expected to cause CNS symptoms (10).

This dose is not outside the realm of quantities that might be absorbed during a prostatic resection. Generally, 10–30 mL/min is absorbed, with volumes up to 6–8 L being absorbed in some cases (12, 13). In a 70-kg patient, this would cause absorption of 1.3–1.7 g/kg of glycine provided a 1.5% solution was used.

Phenobarbital was added to the drinking water in all rats to assure uniformity of control and CCl_4-treated groups. This was discontinued 2 wk before the experiment to allow reversal of hepatic enzyme induction. The duration of the induced state is a function of dose and the inducing agent. A return to basal enzyme activity after phenobarbital withdrawal occurs in 5–7 days (14).

One shortcoming in our study was perhaps that we did not measure serum glycine levels as well as serum ammonia levels. Serum glycine levels were not measured because a standard dose was used in all animals based on animal weight. Whether useful information may have been provided had glycine levels been evaluated is not known. Previous studies have shown that glycine levels peak and are declining as the serum ammonia levels increase. Although this same pattern may have occurred in our study animals, definitive data are lacking. However, in both groups serum ammonia levels did increase after glycine infusion, implying that in both groups of animals glycine was converted to serum ammonia.

Cirrhosis in rats in our study was produced with use of weekly CCl_4 dosing. This model appears to mimic human cirrhosis rather closely, with animals developing liver fibrosis, ascites, hyperbilirubinemia, and portal hypertension (15). Patients with liver dysfunction may occasionally present for TURP, although the subpopulation who are candidates for this procedure will be limited by the presence of coagulation abnormalities.

The ammonia serum levels occurring in cirrhotic animals is a function of the metabolic production and subsequent removal. It seemed likely that, once produced, ammonia would be more slowly cleared by cirrhotic animals because of decreased urea cycle function. However, in the absence of functional liver cells to convert glycine to ammonia, it was previously unclear whether significant production of ammonia would occur. Results of our study show that in cirrhotic rats the ability to metabolically form ammonia from glycine is preserved or certainly much less impaired than is the ability to subsequently remove ammonia from the blood. The kidney is also a site of significant ammonia production from glycine. The liver, however, is the only significant site of metabolic conversion of ammonia to urea. Although we have no direct evidence, it is possible that there were significant renal contributions to the ammonia production from glycine in cirrhotic animals. Evidence of this occurring has been shown by Nathans et al. (16), who found that in hepatectomized dogs, renal ammonia contributions after glycine infusion increased above those seen in normal animals. In our animals with cirrhotic livers, a renal "compensation" may have allowed a more normal biotransformation of infused glycine to ammonia.

Our results indicate that in rats with CCl_4-induced cirrhosis, an exaggerated serum ammonia response occurs after glycine infusion. Interpretation of our data leads us to believe that in the cirrhotic rats, production of ammonia from glycine remains relatively intact, but serum ammonia levels increase to higher levels for a longer time than those in normal rats due to impairment of hepatic urea cycle enzyme inhibition with cirrhosis. Baseline ammonia levels in cirrhotic rats were greater than those in control animals. In a well-managed cirrhotic patient, this abnormality may be lessened by medical management limiting ammonia production, mainly via the intestine. Although the medically well-managed cirrhotic patient might come to surgery with a more normal basal serum ammonia level, after glycine adsorption during prostate resection the resulting ammonia levels once formed would likely remain elevated due to impaired hepatocellular function. If comparable ammonia responses occur in humans with liver dysfunction as in our cirrhotic rats after glycine infusion, prolonged postoperative hyperammonemia may result after TURP if glycine is used in the irrigant solution. Because hyperammonemia plays a role in the etiology of the TURP syndrome in some patients undergoing prostate resection with use of glycine, liver disease may pose an increased risk for postoperative mental abnormalities after prostatic resection. Goodwin (18) suggested that other irrigant solutions such as sorbitol and mannitol be used in patients with liver disease undergoing TURP. Although this suggestion seems prudent, the use of sorbitol in patients with liver disease may also lead to elevated lactate levels after its metabolism (19). Further evaluation of serum ammonia response to glycine absorption in patients with various degrees of liver dysfunction is needed.

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References

1. Roesch RP, Stoelting RK, Lingeman JE, Kahnoski RJ, Backes DJ, Gephardt SA. Ammonia toxicity resulting from glycine absorption during a transurethral resection of the prostate. Anesthesiology 1983;58:577–9.
2. Hoekstra PT, Kahnowski R, McCamish MA, Bergen W, Heetderks DR. Transurethral prostatic resection syndrome—a new perspective: encephalopathy with associated hyperammonemia. J Urol 1983;130:704–7.
3. Hatch PD. Surgical and anaesthetic considerations in transurethral resection of the prostate. Anaesth Intensive Care 1987; 15:203–11.
4. Proctor E, Chatamra K. Controlled induction of cirrhosis in the rat. Br J Exp Pathol 1980;64:320–30.
5. Scheuer PJ. Liver biopsy interpretation. 3rd ed. London: Bailliere Tindall, 1977:117–32.

6. Hulbert BJ, Wingard DW. Water intoxication after fifteen minutes of transurethral resection of the prostate. Anesthesiology 1982;57:332–34.
7. Wakim KG. The pathophysiologic basis for the clinical manifestations and complications of transurethral prostatic resection. J Urol 1961;106:719–28.
8. Pycock CJ, Kerwin RW. The status of glycine as a supraspinal neurotransmitter. Life Sci 1981;28:2679–86.
9. Ovassapian A, Joshi CW, Brunner EA. Visual disturbances: an unusual symptom of transurethral prostatic resection reaction. Anesthesiology 1982;57:332–4.
10. Wang JM, Wong KC, Creel DJ, Clark WM, Shahangian S. Effects of glycine on hemodynamic responses and visual evoked potentials in the dog. Anesth Analg 1985;64:1071–7.
11. Zieve L. The mechanism of hepatic coma. Hepatology 1981; 1:360.
12. Hagstrom RS. Studies of fluid absorption during transurethral prostatic resection. J Urol 1955;73:852–9.
13. Marx GF, Orkin JR. Complications associated with transurethral surgery. Anesthesiology 1962;23:802–13.
14. Casarett LJ, Doull J. Toxicology: the basic science of poisons. 3rd ed. New York: MacMillan, 1986:84–6.
15. Tamayo RP. Is cirrhosis of the liver experimentally produced by CCl_4 an adequate model of human cirrhosis? Hepatology 1983;3:112–20.
16. Nathans D, Fahey JL, Ship AG. Sites of origin and removal of blood ammonia formed during glycine infusion: effect of L-arginine. J Lab Clin Med 1958;51:124–33.
17. Lockwood AH, Mcdonald JM, Reiman RE, et al. The dynamics of ammonia metabolism in man. J Clin Invest 1979;63:449–60.
18. Goodwin WE. Editorial comment. J Urol 1983;130:707.
19. Strunin L. The liver and anaesthesia. In: Major problems in anaesthesia. Volume 3. Philadelphia WB Saunders, 1977.

Passive or Active Inspired Gas Humidification Increases Thermal Steady-State Temperatures in Anesthetized Infants

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BISSONNETTE B, SESSLER DI. Passive or active inspired gas humidification increases thermal steady-state temperatures in anesthetized infants. Anesth Analg 1989;69:783–7.

We tested the hypothesis that active and passive airway humidification minimize hypothermia in infants, but that maintaining normothermia does not decrease the duration of postoperative recovery. A circle system was used to ventilate the lungs of anesthetized, intubated infants who were randomly assigned to active airway humidification and warming with use of an MR450 Servo airway heater and humidifier set at 37°C (n = 10), passive airway humidification with use of the Humid-Vent Mini heat and moisture exchanger placed between the Y-piece of the circle and the endotracheal tube (n = 10), or no airway humidification and heating (control, n = 10). Anesthesia was induced with thiopental and maintained with isoflurane and nitrous oxide in oxygen. The relative humidity of inspired respiratory gases was ~35% in the control group and ~90% in the group undergoing active airway humidification. Initial inspired humidity in the passive humidification group (45%) increased to ~80% after 1 h of anesthesia. Humidity differed significantly across groups at all times ($P \leq 0.05$). Steady-state rectal temperatures (100–120 min after induction) were 36.2 ± 0.7°C in patients given active humidification and heating, 35.7 ± 0.9°C in the passively humidified group, and 35.2 ± 0.4°C in the control group ($P \leq 0.05$ between each group). Recovery from general anesthesia was rapid in all patients and did not correlate with central temperature changes or type of humidification (P = NS). We conclude that heat and moisture exchangers are less effective than active heating and humidification, but significantly better than no humidification.

Key Words: ANESTHESIA, PEDIATRIC. HUMIDIFICATION, INTRAOPERATIVE—pediatric. TEMPERATURE, INTRAOPERATIVE—pediatric.

Airway humidification in intubated patients prevents tracheal damage from dry inspired gases (1), increases tracheal mucus flow (2), and minimizes respiratory heat loss (3,4). Heat and humidity can be added to inspired gases actively by evaporative or ultrasonic humidifiers, or passively, by heat and moisture exchangers ("artificial noses"). Both active and passive gas conditioning minimize intraoperative hypothermia in adults and children, which may speed recovery from general anesthesia (5–8). Active systems increase airway temperature and humidity in children and infants (6) but are expensive, difficult to set up, and associated with complications (9). To determine whether the use of a heat and moisture exchanger having minimal dead space (~2 mL) would benefit infants, we compared central and airway temperatures, airway humidity, thermoregulatory response (cutaneous vasoconstriction), and duration of postanesthetic recovery in infants given active, passive, or no respiratory gas humidification.

Methods

With approval from the Ethical Committee of the Hospital for Sick Children, we studied 30 unpremedicated infants with ASA physical status 1 or 2 after obtaining written, informed consent from their parents. All patients weighed between 5 and 10 kg and were scheduled for peripheral surgery lasting 2–3 h.

We induced anesthesia with thiopental (5 mg/kg) and intubated the trachea of each patient after administration of vecuronium (0.15 mg/kg). A circle system was used to provide ventilation and maintain anes-

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thesia with isoflurane, 1.5 L/min of oxygen, and 3.5 L/min of nitrous oxide. No barbiturates or opioids were given during surgery. Respiratory rate and tidal volume (~10 mL/kg) were adjusted to maintain an end-tidal Pco_2 near 35 mm Hg. Endotracheal tube sizes were chosen to permit an air leak between the tube and the trachea at pulmonary pressures between 15 and 20 cm H_2O, in accordance with current practice. Because gases lost around the endotracheal tube slightly decrease the effectiveness of passive airway humidifiers (10), we maintained peak pulmonary pressures below those required to cause a leak.

The infants were randomly assigned to one of three humidification regimens: *active* airway humidification and warming with an MR450 Servo airway heater and humidifier (Fisher and Paykel Ltd., Auckland, New Zealand) set at 37°C ($n = 10$); *passive* airway humidification achieved by placing the Humid-Vent Mini heat and moisture exchanger (Gibeck Respiration, Inc., Schaumberg, Ill.) between the endotracheal tube adapter of the circle system and the endotracheal tube ($n = 10$); or no airway humidification and heating (*control*, $n = 10$). To assure comparable dead space in all patients, we placed a plastic spacer between the endotracheal tube adapter and the endotracheal tube in the active and control groups. Intravenous fluids were warmed to 37°C, but no other warming techniques were used.

We monitored central (rectal) (11), airway, and skin-surface temperatures with use of disposable thermocouples and model 6500 thermometers (Mon-a-Therm, Inc., St. Louis, Mo.). The rectal probes were inserted to a depth of 5 cm and taped in place. The airway thermocouple was passed through the endotracheal tube and taped in a position estimated to be ~2 cm above the carina (12). Respiratory gas temperatures were measured just before and just after anesthetic gases passed through the heat and moisture exchanger. Thermoregulatory vasoconstriction was evaluated with use of skin-surface temperature gradients (forearm-fingertip) (13,14). Skin-surface temperatures were measured with self-sticking, 1-cm-diameter probes placed midway between the elbow and the wrist on the radial side of an arm without an intravenous line or blood pressure cuff, and on the tip of the index finger of that arm. As in previous studies, we prospectively defined the thermoregulatory threshold for vasoconstriction as the central temperature associated with a skin-temperature gradient ≥4°C (13,14). Thermal steady state (metabolic heat production equal to environmental heat loss) was assumed when rectal temperature no longer changed appreciably (15). Rectal, airway, skin-surface, and ambient temperatures were recorded every 10 min throughout surgery.

Inspired relative humidity was measured with a rapidly responding Humicap (Vaisala, Inc., San José, Calif.) (90% response in <1 s) placed between the Humid-Vent Mini (or spacer) and the endotracheal tube. The Humicap was calibrated with use of saturated and dry gases before and after each application. Induction of anesthesia was defined as time zero, and each variable was first measured at 10 min.

Postoperatively, we administered 5 mL of 0.25% bupivacaine in or around the surgical incision to minimize discomfort during the recovery period. Muscle relaxation was reversed by administration of edrophonium (1 mg/kg) and atropine (40 μg/kg). Patients' tracheas were extubated when each demonstrated sufficient alertness by opening his or her eyes. Ambient temperatures were thermostatically controlled at ~22°C during postanesthetic recovery, and rectal temperatures were recorded every 15–30 min. The presence or absence of shivering-like postoperative tremor was qualitatively evaluated at the same intervals. Fitness for discharge was based on standard criteria including (a) rectal temperature ≥36°C; (b) recovery period ≥30 min; (c) patient alert with stable vital signs; and (d) no surgical problems. Patients were released from the recovery area by an anesthesiologist blinded to the method of airway humidification.

Differences among groups were compared with use of one-way analysis of variance and Student-Newman-Keuls tests and were considered statistically significant when $P < 0.05$. Results are presented as mean ± SD.

Results

The three study groups did not differ significantly in mean age, weight, gender, end-tidal concentrations of CO_2 or isoflurane, or intraoperative ambient temperature (Table 1). The types of surgery also did not differ markedly. Most were hypospadias repairs or minor urologic procedures.

The relative humidity of the inspired gases was ~90% in patients given active airway humidification and ~35% in those given unconditioned gases (Figure 1). Passive humidification increased airway humidity from approximately 45% at the beginning of anesthesia to approximately 80% after 1 h. Humidity differed significantly among the groups at all times. The temperature difference across the Humid-Vent Mini was 7.6 ± 1.8°C (mean ± SD) and did not change as a function of time.

Table 1. Mean Age, Weight, Ambient Temperature During Surgery, End-tidal CO_2 and Isoflurane Concentrations, and Duration of Postanesthetic Recovery in Patients Assigned to Receive Active, Passive, or no Airway Humidification

	Control	Passive	Active
Number	10	10	10
Age (mo)	10.0 ± 5.0	12.3 ± 5.9	11.2 ± 4.2
Weight (kg)	7.8 ± 2.5	8.1 ± 2.0	8.5 ± 1.7
Number of male patients	8	7	9
End-tidal CO_2	36 ± 1	36 ± 2	35 ± 2
End-tidal isoflurane	1.1 ± 0.1	1.2 ± 0.2	1.0 ± 0.1
Intraoperative ambient temperature (°C)	20.3 ± 0.8	20.6 ± 0.6	20.7 ± 0.9
Recovery time (min)	75 ± 35	84 ± 27	78 ± 25

All values are mean ± SD. There were no statistically significant differences between the groups.

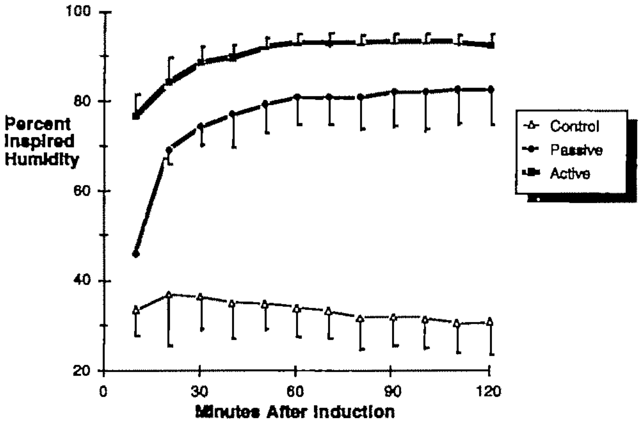

Figure 1. Mean inspired relative humidity in 30 infants and children given active (n = 10), passive (n = 10), or no airway humidification (n = 10). *Vertical bars* illustrate standard deviation. Humidity in each of the groups differed significantly at all times ($P < 0.05$).

Mean intraoperative rectal temperatures decreased 0.5 ± 0.7°C during active airway humidification, 1.0 ± 0.7°C during passive humidification, and 1.3 ± 0.6°C during no humidification (Figure 2). From 80 to 120 min, rectal temperatures in the active and control groups differed significantly; temperatures in the passive group did not differ from those in the other groups at any time.

Rectal temperature curves indicated that temperatures did not change appreciably after 90 min of anesthesia, which allowed us to average intragroup temperatures between 100 and 120 min after induction to determine steady-state temperature. Thermal steady state differed significantly across groups, being 36.2 ± 0.7°C in the active group, 35.7 ± 0.9°C in the passive group, and 35.2 ± 0.4°C in control patients.

Intraoperative thermoregulatory vasoconstriction (forearm-fingertip gradient ≥4°C) was observed in the second coldest patient in each group, at a mean rectal temperature of 34.8 ± 0.4°C and an end-tidal isoflurane concentration of 1.03% ± 0.06%.

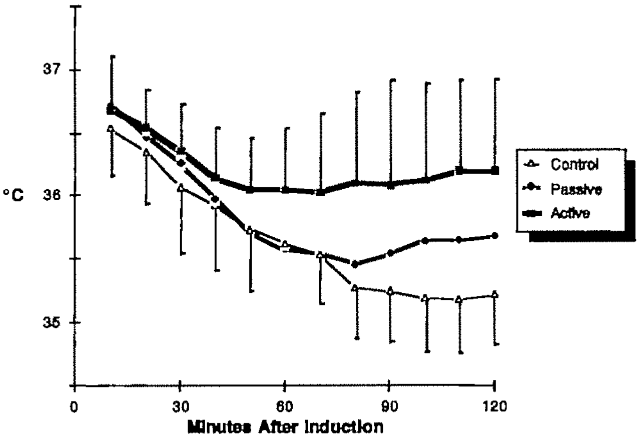

Figure 2. Mean rectal temperatures decreased 0.5 ± 0.7°C in patients given active airway humidification, 1.0 ± 0.7°C in those given passive humidification, and 1.3 ± 0.6°C in the control group. *Vertical bars* illustrate standard deviation. Standard deviations of the group given passive intraoperative humidification (omitted for clarity) were similar to those of the children given actively humidified respiratory gases. From 80 to 120 min, temperatures in the active and control groups were significantly different; the passive group was not significantly different from any other group at any time. Temperatures between 100 and 120 min after induction were averaged within each group to determine steady-state temperatures. Thermal steady state differed significantly among the groups, being 36.2 ± 0.7°C in the active group, 35.7 ± 0.9°C in the passive group, and 35.2 ± 0.4°C in patients given no airway humidification.

Mean intraoperative airway temperatures (measured ~2 cm above the carina) in the control group were significantly lower than those in the active group at all times; temperatures in the passive group differed significantly from the control group after 40 min of anesthesia, but never significantly from those in the active group (Figure 3).

Postoperatively, no children required analgesics before discharge from the recovery area. One patient in each group developed shivering-like postoperative tremor for a total of five observation epochs. Tremor occurred at a mean rectal temperature of 36.0 ± 0.8°C but was observed in one patient whose temperature was 37.0°C. Postoperative mean rectal temperatures are provided in Figure 4. Children in each group rewarmed at ~0.9°C/h (P = NS) and the mean duration of recovery from anesthesia did not differ significantly among groups (Table 1). All patients but one remained in the recovery area at least 60 min.

Discussion

Humidification increased over time in the patients given passively humidified respiratory gases. Most

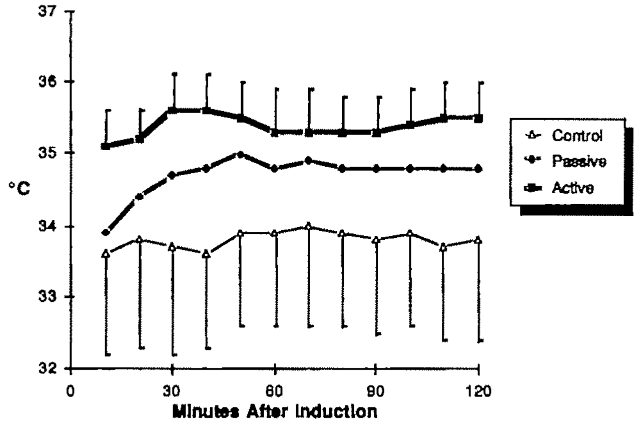

Figure 3. Mean airway temperatures (measured ~2 cm above the carina). Standard deviations of the group given passive intraoperative humidification (omitted for clarity) were similar to those of the children given actively humidified respiratory gases. Carinal temperatures in the control group were significantly lower than those in the active group at all times; temperatures in the passive group differed significantly from the control group after 40 min of anesthesia and were never significantly different from those in the active group.

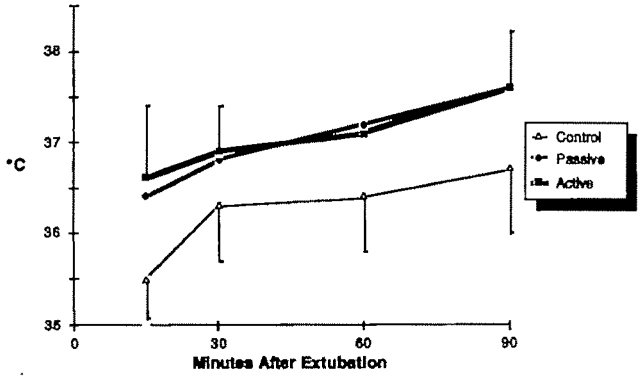

Figure 4. Mean rectal temperatures during the recovery from isoflurane anesthesia. Standard deviations of the group given passive intraoperative humidification (omitted for clarity) were similar to those of the children given actively humidified respiratory gases during surgery. Children in each group rewarmed at ~0.9°C/h (P = NS).

heat and moisture exchangers (including the Humid-Vent Mini) use a hygroscopic membrane to trap expired heat and moisture. Even the small humidifier we used (~2-mL internal volume) required nearly 1 h to achieve full saturation (thus provide maximal effect). Adult-sized filters would provide a greater heat and moisture reservoir, but have too large a dead-space for use in infants and might saturate too slowly to be effective. Both active and passive airway humidification provided >50% relative humidification, the amount needed to prevent ciliary damage (1,2).

Thermal steady state (constant mean body temperature) occurs when environmental heat loss equals metabolic heat production. Steady state can be passive or result from physiologic regulation of heat production or heat loss, or both. Active regulation in anesthetized adults occurs when hypothermia is sufficient to trigger thermoregulatory responses, usually about 34.5°C (the regulatory threshold depends on the type of anesthesia and the dose administered) (13,14,16). Only one infant in each group demonstrated significant thermoregulatory vasoconstriction, at a mean temperature of 34.8 ± 0.4°C. Thermal steady state was passive in the other patients.

After ~90 min of anesthesia, central temperatures stabilized at significantly different values. Because all groups had similar types of surgery under similar environmental conditions, the significant difference in steady-state temperature across groups was determined primarily by the type of respiratory gas conditioning. As expected from previous studies in children (6), steady-state temperatures were highest in patients whose respiratory gases were actively warmed and lowest in those given unconditioned gases. These data indicate that passive gas humidification and warming is less effective than active conditioning, but significantly better than no treatment.

Humidity measured between the Humid-Vent Mini (or spacer) and the endotracheal tube varies considerably on a breath-by-breath basis. No currently available humidity monitor responds rapidly enough to provide accurate measurements throughout the entire respiratory cycle. Therefore, exact water (and thus heat) loss cannot be determined, even when a Humicap is paired with a pneumotachometer. Nonetheless, the relatively simple technique used in this study demonstrated that both passive and active methods adequately humidified the airway to prevent tracheal mucosal damage.

Recovery was rapid in all patients and did not correlate with central temperature or type of humidification. Although one study in adults demonstrated a significantly shorter recovery period in patients given active airway humidification (7), subsequent studies did not identify a difference (8). Airway humidification in children also seems to have little effect on the duration of recovery (6). The results of this study indicate that infants are similar to children and adults in that duration of postoperative recovery is minimally influenced by airway humidification.

Although we evaluated only patients anesthetized with isoflurane and nitrous oxide, it is unlikely that a physical process such as respiratory heat loss is significantly influenced by anesthetic drugs. However, our patients were generally healthy, weighed 5–10 kg, and underwent peripheral surgery. Although temperature changes will differ in other patient populations, respiratory heat and moisture losses would be similar. Additionally, anesthetic circuit design changes airway humidity (17), but the changes are smaller than generally expected (18).

In summary, 30 infants and children were randomly assigned to active, passive, or no intraoperative airway humidification and warming. Active airway heating and humidification provided most airway warming and inspired gas humidification, but the Humid-Vent Mini heat and moisture exchanger was nearly as effective. Active humidification was most effective in minimizing central hypothermia, but the heat and moisture exchanger was significantly better than no humidification. Recovery was rapid in all patients and did not correlate with central temperature or type of humidification. Heat and moisture exchangers appear to be a reasonable alternative to active airway humidification in infants. They immediately supply enough humidity to prevent tracheal damage and, after ~1 h of anesthesia, provide a relative humidity similar to that of active systems.

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References

1. Chalon J, Patel C, Ali M, et al. Humidity and the anesthetized patient. Anesthesiology 1979;50:195–8.
2. Forbes AR. Temperature, humidity and mucus flow in the intubated trachea. Br J Anaesth 1974;46:29–34.
3. Tollofsrud SG, Gundersen Y, Andersen R. Peroperative hypothermia. Acta Anaesthesiol Scand 1984;28:511–5.
4. Berry FA Jr, Hughes-Davies DI, DiFazio CA. A system for minimizing respiratory heat loss in infants during operation. Anesth Analg 1973;52:170–5.
5. Haslam KR, Nielsen CH. Do passive heat and moisture exchangers keep the patients warm? Anesthesiology 1986;64:379–81.
6. Bissonnette B, Sessler DI, LaFlamme P. Passive and active inspired gas humidification in infants and children. Anesthesiology 1989;71:381–4.
7. Conahan TJ III, Williams GD, Apfelbaum JL, Lecky JH. Airway heating reduces recovery time (cost) in outpatients. Anesthesiology 1987;67:128–30.
8. Conahan TJ III, Kitz DS, Andrews RW, Lecky JH. Airway heating does not affect recovery time or postoperative complaints in outpatients (abstr). Anesthesiology 1988;69:A278.
9. Klein EF Jr, Graves SA. "Hot pot" tracheitis. Chest 1974;65:225–6.
10. Tilling SE, Hayes B. Heat and moisture exchangers in artificial ventilation. An experimental study of the effect of gas leakage. Br J Anaesth 1987;59:1181–8.
11. Bissonnette B, Sessler DI, LaFlamme P. Temperature monitoring sites in infants and children. Anesth Analg 1989;69:192–6.
12. Dery R, Pelletier J, Jacques A, Clavet M, Houde JJ. Humidity in anaesthesiology III. Heat and moisture patterns in the respiratory tract during anaesthesia with the semi-closed system. Can Anaesth Soc J 1967;14:287–98.
13. Sessler DI, Olofsson CI, Rubinstein EH, Beebe JJ. The thermoregulatory threshold in humans during halothane anesthesia. Anesthesiology 1988;68:836–42.
14. Sessler DI, Olofsson CI, Rubinstein EH. The thermoregulatory threshold in humans during nitrous oxide-fentanyl anesthesia. Anesthesiology 1988;69:357–64.
15. Sessler DI, Rubinstein EH. Core temperature changes during N_2O/fentanyl and halothane/O_2 anesthesia. Anesthesiology 1987;67:137–9.
16. Støen R, Sessler DI. The thermoregulatory threshold is inversely proportional to isoflurane concentration. Anesthesiology (in press).
17. Weeks DB. A laboratory evaluation of recently available heat-and-moisture exchangers. Anesthesiol Rev 1986;13:33–6.
18. Aldrete JA, Cubillos P, Sherrill D. Humidity and temperature changes during low flow and closed system anaesthesia. Acta Anaesthesiol Scand 1981;25:312–4.

Intraneural Recording of Muscle Sympathetic Activity During Epidural Anesthesia in Humans

Stefan Lundin, MD, PhD, B. Gunnar Wallin, MD, and Mikael Elam, MD, PhD

LUNDIN S, WALLIN BG, ELAM M. Intraneural recording of muscle sympathetic activity during epidural anesthesia in humans. Anesth Analg 1989;69:788–93.

The extent and magnitude of sympathetic blockade during epidural anesthesia have previously been assessed only by indirect methods. In this study, direct intraneural recordings of muscle sympathetic activity (MSA) in the peroneal nerve was performed to determine the profundity of blockade of sympathetic fibers to the lower extremities during epidural anesthesia. Lumbar epidural catheters were inserted in nine volunteers. Multiunit postganglionic sympathetic activity was recorded in a muscle fascicle of the peroneal nerve before and after epidural injection of 4 mL of 2% mepivacaine followed by an additional 12–16 mL after 5 min. Apnea (30–60 s) was used to elicit transient sympathetic activation. The upper level of sensory blockade was T-3 to T-10. Muscle sympathetic activity decreased after epidural blockade with no spontaneous or apnea-induced sympathetic bursts observed later than 11 min after injection of the initial test dose. Sympathetic blockade was accompanied by increase in foot skin blood flow as well as loss of skin resistance responses to arousal. Results show that epidural anesthesia with sensory blockade above T-10 to T-11 blocks spontaneous peroneal MSA as well as the marked sympathetic activation induced by apnea.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—sympathetic block.

Introduction

The profundity and extent of sympathetic blockade accompanying regional anesthesia are a matter of controversy (1). A number of indirect methods monitoring sympathetic effector organ function have been used to evaluate changes of sympathetic activity during regional anesthesia. Sudomotor function has been assessed with sweat tests (2) and recordings of skin resistance (3), whereas peripheral vasomotor function has been monitored with use of digital pulse-wave measurements (4), laser Doppler flowmetry (5), xenon 133 clearance (6), skin temperature recordings (6,7), and measurements of central hemodynamics (8,9).

It has been suggested (10) that epidural anesthesia is associated with a reduction in sympathetic neural traffic rather than with a complete blockade of sympathetic fibers. Based on studies of skin resistance changes as an index of efferent sympathetic nerve activity, it has also been claimed that both epidural and spinal anesthesia may have a poor blocking effect even on sympathetic outflow to the lower extremities (11). To test this notion, we have made direct intraneural recordings of muscle sympathetic activity (MSA) in the peroneal nerve in humans during epidural anesthesia. Apnea tests were used to transiently increase sympathetic nerve activity and challenge the neurogenic blockade. Changes in skin blood flow and skin resistance were also monitored in some subjects to assess changes in cutaneous sympathetic effector organ function.

Methods

Experiments were performed on nine healthy volunteers, eight men and one woman, aged 24–39 yr.

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Written informed consent was given by all subjects and the investigation was approved by the Human Ethics Committee, University of Göteborg.

Recording of Muscle Sympathetic Nerve Activity

Multiunit efferent postganglionic sympathetic activity was recorded with use of a tungsten microelectrode with a tip diameter of a few microns, inserted in a muscle fascicle of the peroneal nerve at the fibular head. A reference electrode was inserted subcutaneously 1–2 cm away from the recording electrode. When a muscle nerve fascicle had been identified (see below), small electrode adjustments were made until a site was found in which sympathetic impulses could be recorded. Criteria for muscle sympathetic activity were (a) weak electrical stimulation (0.5–1.5 V, 0.2 s, 1 Hz) through the intraneural electrode elicited involuntary muscle contractions but not cutaneous paresthesia; (b) tapping or stretching of the muscle innervated by the impaled fascicle elicited afferent mechanoreceptor discharges, whereas stroking the skin within the distribution area of the peroneal nerve did not evoke afferent impulses; and (c) the neurogram displayed spontaneous intermittent and pulse synchronous bursts characteristic of MSA. Evidence for the sympathetic nature of this activity has been established previously (12) and include (a) blockage of nerve activity by injection of lidocaine around the nerve proximal to the recording point but not by injection distal to the recording point, proving that the impulses are efferent; (b) conduction velocities of ~1 m/s, a value typical of sympathetic fibers; and (c) reversible blockage of impulse traffic along the nerve by intravenous ganglionic blockers.

The original nerve signal was fed through a band pass filter with a band width of 700–2000 Hz. Both filtered and mean voltage neurograms [obtained by passing the filtered neurogram through a resistance-capicatance (RC) integrating network with a time constant of 0.1 s] were stored together with records of electrocardiography, skin blood flow, galvanic skin response (GSR), and respiratory movements on an FM tape recorder (Sangamo Sabre VI; Sangamo-Weston Schlumberger, Sarasota, Fla.). All variables recorded were also displayed on an ink-jet recorder (modified Mingograph 800; Siemens-Elema Ltd., Solna, Sweden) with a paper speed of 3 mm/s. Records were divided into 1-min periods and, for each period, the number of pulse synchronous bursts in the mean voltage neurogram was counted and the nerve activity was expressed as bursts per minute. Measurements of burst amplitudes were also made from the chart and expressed as mean burst amplitude per minute in percent of the mean value during the 8-min baseline period.

Skin Blood Flow Measurements

In five subjects, skin blood was monitored continuously with use of laser Doppler flowmetry (Periflux; Perimed AB, Stockholm, Sweden) with a frequency limit of 4 kHz and a time constant of 0.2 s. Electrical calibration for zero blood flow was made in all recordings. Several gains for the analogue output were available via switches. The maximal output of a given gain level (defined electrically) was taken as 100%. The analogue output of the flowmeter gives no absolute value but shows relative changes of the flux of red blood cells (for technical details and evaluation of the laser Doppler flowmeter, see References 13–15). The laser Doppler probe was placed on the plantar side of the great toe of the leg used for MSA recording.

Galvanic Skin Response

In four subjects, changes in skin resistance to arousal stimuli (see Procedure and References 11 and 12) were monitored by modified van Gough GSR modules (type IGSR/7A AC coupled). Silver/silver chloride (Ag/AgCl) electrodes were fixed to glabrous skin both on the foot and on the hand ipsilateral to the MSA recordings.

Blood pressure and heart rate were measured automatically every 3–5 min by sphygmomanometry (Nippon Colin, Sphygmomanometer BP-203, W. A. Baum Co., Inc.) from the left arm at heart level. An electrocardiogram was recorded by surface electrodes on the chest, and respiratory movements were monitored with a strain gauge attached to a rubber strap around the chest.

Procedure

The subjects received no premedication or intravenous fluids. Significant hypotension (systolic pressure <90 mm Hg) was treated with ephedrine (10 mg IV). After filtration of the skin with 2 mL of 1% mepivacaine, epidural puncture was performed at the L2–3 or L3–4 interspace and an epidural catheter was inserted 3–4 cm into the epidural space. With the subjects in a comfortable supine position, continuous recordings of electrocardiograms, respiratory movements, blood pressure, heart rate, GSR, and skin

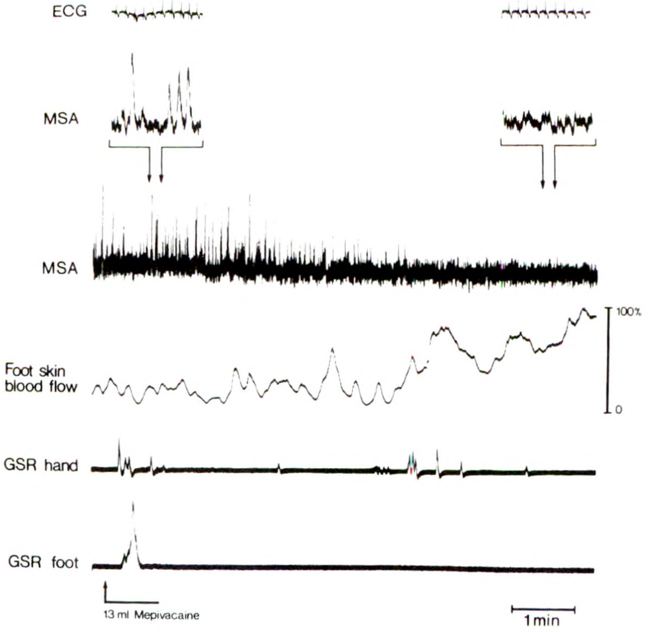

Figure 1. Muscle sympathetic activity (MSA) from the left peroneal nerve, skin blood flow in the left big toe, and galvanic skin responses (GSR) in the left hand and foot during the initial stage of epidural anesthesia with 2% mepivacaine. Note the characteristic pulse-synchronous sympathetic bursts in the mean voltage neurogram. A 4-mL test dose (not shown) was given 5 min before the 13-mL dose. The decrease in MSA had started before the second injection. No detectable sympathetic bursts occurred later than 11 min after the test dose. Note that GSRs were abolished in the foot but were unaltered in the hand during the blockade. The increase in skin blood flow that started ~6 min after the test dose became maximal 20 min after the test dose (not shown).

blood flow were initiated. Subsequently, the peroneal nerve was located at the fibular head and a recording of MSA initialized. Baseline sympathetic activity was recorded for 8 min after which a test dose of 4 mL of 2% mepivacaine solution was injected epidurally, followed 5 min later by an additional bolus dose (adjusted to age) of 12–16 mL (13.4 ± 0.4 mL). Upper level of sensory blockade on the same side of the body as the nerve recording was determined as the most cephalad dermatome at which analgesia to pinprick occurred. During epidural blockade, afferent mechanoreceptor discharge (evoked by tapping or stretching the muscle innervated by the impaled fascicle) was tested at intervals and used as a criterion for unaltered electrode position.

Maximal voluntary apnea (30–60 s in duration), a procedure that markedly increases muscle sympathetic discharge, was performed before, during, and after epidural anesthesia to challenge the neurogenic blockade. Arousal stimuli such as sudden unexpected sounds or touches were used intermittently to elicit changes in skin resistance (GSR).

Statistics

Values are presented as mean ± SEM. The Wilcoxon sign rank test was used for statistical analyses. The level of $P < 0.05$ was chosen for statistical significance for all tests.

Results

The maximal upper segmental levels of sensory blockade obtained 30–45 min after the test dose were T-7 ± 1 and ranged from T-3 to T-10. Epidural blockade was associated with a slight increase (NS) in heart rate from 63 ± 2 beats/min before to 68 ± 3 beats/min 30 min after the test dose. Systolic blood pressure decreased from 120 ± 2 mm Hg before to 113 ± 3 mm Hg ($P < 0.05$) 30 min after the test dose. The decrease in diastolic pressure was from 71 ± 2 to 67 ± 2 mm Hg (NS). In one subject (with a sensory block to T-3) ephedrine (10 mg IV) was given 14 min after the test dose because of a decrease in blood pressure to 85/45 mm Hg.

Figure 1 shows a typical recording of muscle sympathetic activity, skin blood flow, and changes in skin resistance during the development of epidural blockade in one subject. In each subject, the basal level of MSA remained fairly constant during the 8-min baseline period, but the level differed markedly between subjects (mean, 37 ± 4 bursts/min; range, 20–51 bursts/min; $n = 9$). Soon after the test dose of local anesthetic was injected epidurally, the number of sympathetic bursts started to decrease and no detectable sympathetic activity remained 8 ± 1 min (range, 5–11) after the test dose, i.e., 0–6 min after the full dose. Findings were similar in all subjects ($n = 9$), and Figure 2 shows the time-course of the effects for the number of bursts per minute (left) and mean burst amplitudes (right).

Apnea before, during, and after the blockade transiently increased sympathetic activity and challenged the neurogenic blockade (Figure 3). Before the epidural block, marked increases in all subjects were observed in the number of sympathetic bursts and in their mean voltage amplitude toward the end of a 30–60-s apnea. During the blockade, no detectable sympathetic activity was provoked by apnea later than 11 min after the test dose, i.e., 6 min after the full dose of epidural mepivacaine.

Loss of afferent mechanoreceptor discharge (tested by tapping or stretching the muscle innervated by the impaled fascicle), indicating a change in electrode position, occurred in five MSA recordings 19, 39, 69, 71, and 86 min after the test dose, respectively. In the remaining four subjects, there was a gradual return of

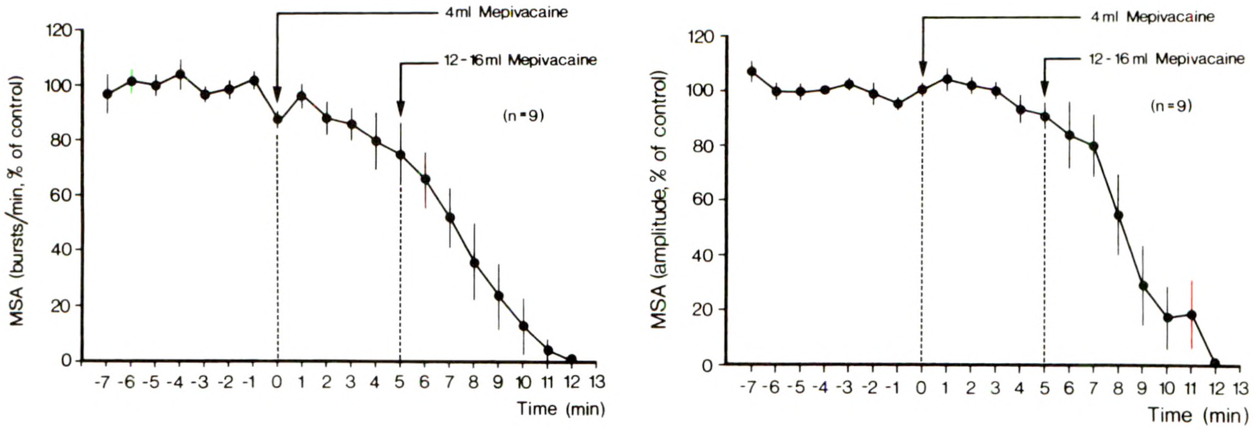

Figure 2. The effect of epidural mepivacaine anesthesia on muscle sympathetic activity (MSA) as measured by the number of spontaneous pulse-synchronous sympathetic bursts per minute (*left panel*) and their mean voltage amplitudes (*right panel*). Results are expressed as a percentage of the mean value during the 8-min control period and represent mean ± SEM (n = 9). The test dose was injected at 0 min and the second dose at 5 min.

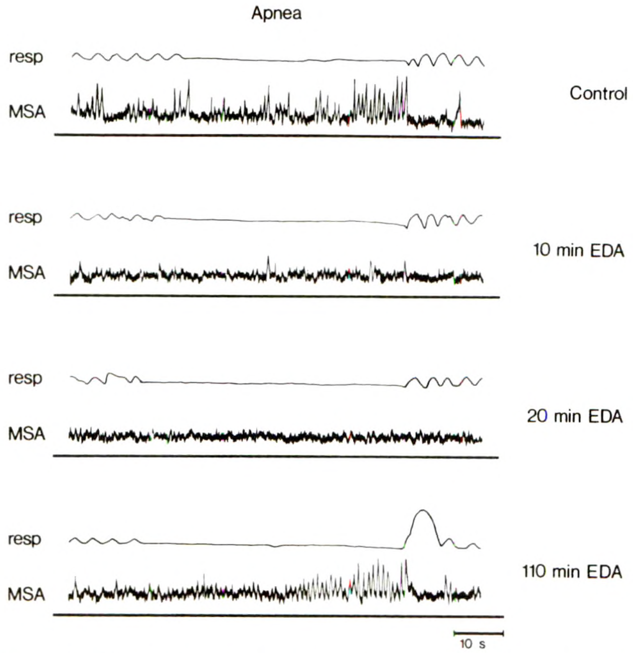

Figure 3. Effects of epidural mepivacaine anesthesia on spontaneous muscle sympathetic activity (MSA) and the MSA response during apnea. Note the successive decrease in MSA 10 and 20 min after epidural mepivacaine including loss of apnea-induced excitation. The *lower trace* shows the return of spontaneous MSA and apnea-induced activation, concomitant with regression of sensory blockade to T-11.

MSA with the first spontaneous sympathetic bursts occurring 66, 83, 97, and 115 min after the test dose, respectively (Figure 3). At that time, upper segmental levels of the sensory blockade had regressed to T-11 (three subjects) and T-10 (one subject). After regression of the epidural blockade, apnea-induced sympathetic activation returned in all four subjects (Figure 3).

As illustrated in Figure 1, skin blood flow started to increase 5.0 ± 0.3 min after the test dose (n = 5). The maximal increase in skin blood flow was reached 20 ± 2 min after the test dose when blood flow was 11 ± 3 times higher than the baseline levels.

Before epidural blockade, arousal stimuli evoked typical decreases in skin resistance in both the foot and the hand (Figure 1). Epidural blockade, with an upper maximal sensory level of T-3 to T-9, was associated with loss of GSRs to arousal stimuli in the foot but not in the hand in all four subjects tested.

Discussion

We found that epidural anesthesia with a maximal upper level of sensory blockade at T-3 to T-10 eliminated spontaneous MSA in the peroneal nerve and abolished the sympathetic activation induced by apnea. The anesthesia was accompanied by increased skin blood flow and loss of GSRs to arousal in the foot but not in the hand.

It has been shown previously (16) that in a given subject the number of sympathetic bursts per minute in muscle nerves is remarkably constant not only during a whole experiment but even when recordings are repeated at intervals of weeks and months. Also in the present study, sympathetic activity was stable during the 8-min baseline period, whereas the anesthesia induced a successive disappearance of MSA starting within 5 min of the injection of the test dose of mepivacaine. In the four subjects in whom the recording site was maintained, sympathetic nerve traffic returned as anesthesia wore off. These findings show conclusively that the disappearance of MSA after the mepivacaine injection was not an artifact due to loss of the recording site.

The concept (17,18) that epidural and spinal anesthesia result in a complete block of sympathetic nerve activity of at least the same extent as that of the sensory block has been questioned (3,5,10,11). Bromage (10) stated that epidural blockade usually is not a complete block of sympathetic fibers but merely a reduction in neural traffic. This view was based on recordings of sympathetic end-organ activities as markers of changes in neural traffic (see Introduction). It was suggested that "idle" efferent sympathetic fibers escaping epidural blockade within the segmental territory of sensory blockade could be recruited after an increase in vasomotor activity within the central nervous system (10). Based on studies using recordings of skin resistance changes as an index of efferent sympathetic changes, it has also recently been suggested (11) that both epidural and spinal anesthesia may have a poor blocking effect even on sympathetic outflow to the lower extremities. In our multiunit recordings of sympathetic activity, no impulses were seen in original or mean voltage neurograms either at rest or during the apnea, which before blockade induced a powerful sympathetic activation. In addition, during the anesthesia no cutaneous sympathetic effector responses to arousal were evoked in the foot, although they did occur in the hand. Together these findings show that the sympathetic fibers to the lower extremities were completely blocked when sensory anesthesia was present up to or above the T-10 level.

Studies on the autonomic effects of spinal anesthesia have given variable results. Chamberlain and Chamberlain (7) observed that spinal anesthesia led to temperature elevations in six to seven segments above the level of sensory blockade, i.e., results suggesting that the sympathetic block was more widespread than the sensory one. One should remember, however, that changes of skin temperature provide a complex measure of sympathetic function, especially when core temperature changes. Furthermore, the regulation of skin blood flow varies markedly with variations in ambient temperature (18). In contrast to the results of Chamberlain and Chamberlain (7), Bengtsson et al. (3) and Malmqvist et al. (19), in evaluating sympathetic blockade by monitoring skin conductance responses, reported that spinal anesthesia (upper sensory level T-4 to T-6) produced complete blockade of sympathetic fibers to the foot in only 60% of patients. Future studies with recordings of skin resistance changes to arousal, together with direct recordings of sympathetic activity, are needed to further investigate the degree of sympathetic blockade during spinal anesthesia.

With one exception, the epidural blockade in the present study was associated with only modest changes in blood pressure and heart rate. It seems likely that hemodynamic stability was maintained by compensatory vasoconstriction cephalad to the area of sympathetic blockade (20). This emphasizes the difficulty in drawing conclusions about the profundity or extent of sympathetic blockade from measurements of central hemodynamics (8–10), particularly because the systemic effects of the local anesthetic may contribute to the circulatory changes seen during epidural anesthesia (21).

In conclusion, this study shows that epidural anesthesia with 2% mepivacaine with a sensory blockade above the T-10 to T-11 level is associated with a complete blockade of sympathetic fibers to the lower extremities as measured by intraneurally recorded MSA in the peroneal nerve. The sympathetic blockade was paralleled by skin vasodilation and a loss of sudomotor function within the anesthetized area.

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References

1. Greene NM. A new look at sympathetic denervation during spinal anesthesia. Anesthesiology 1986;65:137–8.
2. Dhunér KG, Edshage S, Wilhelm A. Ninhydrin test—an objective method for testing local anaesthetic drugs. Acta Anaesthesiol Scand 1960;4:189–98.
3. Bengtsson M, Löfström JB, Malmqvist LÅ. Skin conductance responses during spinal analgesia. Acta Anaesthesiol Scand 1985;29:67–71.
4. Kim JM, LaSalle AD, Parmley RT. Sympathetic recovery following lumbar epidural and spinal analgesia. Anesth Analg 1977;56:352–5.
5. Bengtsson M, Nilsson GE, Löfström JB. The effect of spinal analgesia on skin blood flow, evaluated by laser Doppler flowmetry. Acta Anaesthesiol Scand 1983;27:206–10.
6. Cousins MJ, Wright CJ. Graft, muscle, skin blood flow after epidural block in vascular surgical procedures. Surg Gynecol Obstet 1971;133:59–64.
7. Chamberlain DP, Chamberlain BDL. Changes in the skin temperature of the trunk and their relationship to sympathetic blockade during spinal anesthesia. Anesthesiology 1986; 65:139–43.
8. Bonica JJ, Berges PU, Morikawa K. Circulatory effects of peridural block: 1. Effects of level of analgesia and dose of lidocaine. Anesthesiology 1970;33:619–26.
9. Scott DB, Littlewood DG, Drummond GB, Buckley BF, Covino BG. Modification of the circulatory effects of extradural block combined with general anesthesia by the addition of adrenaline to lignocaine solutions. Br J Anaesth 1977;49:917–25.

10. Bromage PR. Epidural analgesia. Philadelphia: WB Saunders, 1978:347–442.
11. Löfström JB, Cousins MJ. Sympathetic neural blockade of upper and lower extremities. In: Neural blockade in clinical anesthesia and management of pain, 2nd ed. Philadelphia: JB Lippincott, 1988:461–500.
12. Vallbo ÅB, Hagbarth KE, Torebjörk HE, Wallin BG. Somatosensory, proprioceptive and sympathetic activity in human peripheral nerves. Physiol Rev 1979;59:919–57.
13. Holloway GA, Watkins DW. Laser-Doppler measurements of cutaneous blood flow. J Invest Dermatol 1977;69:306–9.
14. Nilsson GE, Tenland T, Öberg PA. Evaluation of a laser Doppler flowmeter for measurement of tissue blood flow. IEEE Trans Biomed Eng 1980;27:507–604.
15. Johnson JM, Taylor WF, Shepherd P, Park MK. Laser-Doppler measurements of skin blood flow: comparison with plethysmography. J Appl Physiol 1984;56:789–803.
16. Sundlöf G, Wallin BG. Human muscle nerve sympathetic activity at rest. Relationship to blood pressure and age. J Physiol (Lond) 1978;274:621–37.
17. Takeshima R, Dohi S. Circulatory responses to baroreflexes, valsalva maneuver, coughing, swallowing, and nasal stimulation during acute sympathectomy by epidural blockade in awake humans. Anesthesiology 1985;63:500–8.
18. Oberle J, Elam M, Karlsson T, Wallin BG. Temperature-dependent interaction between vasoconstrictor and vasodilator mechanisms in human skin. Acta Physiol Scand 1988; 32:459–69.
19. Malmqvist LA, Bengtsson M, Björnsson G, Jordfeldt L, Löfström JB. Sympathetic activity and hemodynamic variables during spinal analgesia in man. Acta Anaesthesiol Scand 1987;31:467–73.
20. Sjögren S, Wright B. Circulation, respiration and lidocaine concentration during continuous epidural blockade. Acta Anaesthesiol Scand 1972;16:5–25.
21. Wattwil M, Sundberg A, Arvill A, Lennquist C. Circulatory changes during high thoracic epidural anesthesia—influence of sympathetic block and of systemic effect of the local anaesthetic. Acta Anaesthesiol Scand 1985;29:849–55.

Comparative Systemic Toxicity of Convulsant and Supraconvulsant Doses of Intravenous Ropivacaine, Bupivacaine, and Lidocaine in the Conscious Dog

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FELDMAN HS, ARTHUR GR, COVINO BG. Comparative systemic toxicity of convulsant and supraconvalsant doses of intravenous ropivacaine, bupivacaine, and lidocaine in the conscious dog. Anesth Analg 1989;69:794-801.

This study evaluated the systemic toxicity, arrhythmogenicity, and mode of death of convulsant and supraconvulsant doses of lidocaine, bupivacaine, and ropivacaine. Experiments in awake dogs were designed to mimic the clinical situation of an accidental intravenous (IV) injection of local anesthetics.

On the first experimental day, lidocaine (8 mg·kg^{-1}·min^{-1}), bupivacaine (2 mg·kg^{-1}·min^{-1}), and ropivacaine (2 mg·kg^{-1}·min^{-1}) were infused intravenously until seizures occurred (n = 6 for each group). The average dose and arterial plasma concentration at seizure onset was 20.8 ± 4.0 mg/kg and 47.2 ± 5.4 μg/mL for lidocaine, 4.31 ± 0.36 mg/kg and 18.0 ± 2.7 μg/mL for bupivacaine, and 4.88 ± 0.47 mg/kg and 11.4 ± 0.9 μg/mL for ropivacaine.

The margin of safety between the convulsive and lethal doses was determined by administering two times the convulsive dose 24 h later. Two dogs given lidocaine died because of progressive hypotension, respiratory arrest, and finally cardiovascular collapse with an average peak plasma concentration (C_{max}) of 469 μg/mL. No ventricular arrhythmias were observed in this group. Ventricular arrhythmias occurred in five of six dogs receiving bupivacaine. Four animals died because of hypotension, respiratory arrest, and cardiovascular collapse. One additional animal died because of ventricular fibrillation. The C_{max} for bupivacaine was 70.1 ± 14.6 μg/mL in nonsurvivors. In the ropivacaine group one animal died because of hypotension, respiratory arrest, and cardiovascular collapse (C_{max} = 72.4 μg/mL). A surviving dog had transient premature ventricular contractions.

Twenty-four hours later three times the convulsive dose was administered to the survivors. Death occurred in three animals in the lidocaine group, the remaining dog in the bupivacaine group, and four dogs in the ropivacaine group. All deaths were due to hypotension, respiratory arrest, and subsequent cardiovascular collapse. Ventricular arrhythmias were observed in two dogs in the ropivacaine group and the single dog receiving bupivacaine. The results suggest that the convulsive doses for ropivacaine and bupivacaine are similar. However, ropivacaine may possess a greater margin of safety and be less arrhythmogenic than bupivacaine after an accidental rapid IV injection. Only lidocaine was devoid of arrhythmogenic activity.

Key Words: ANESTHETICS, LOCAL, TOXICITY—bupivacaine, ropivacaine, lidocaine. TOXICITY, LOCAL ANESTHETICS—bupivacaine, ropivacaine, lidocaine.

Bupivacaine has been implicated in the production of ventricular arrhythmias and cardiovascular collapse in humans (1–4). In vivo and in vitro laboratory studies indicate that bupivacaine may be more cardiotoxic than other local anesthetics such as lidocaine when equipotent anesthetic doses are utilized (5–12). The data also suggest that the margin of safety between the onset of central nervous system (CNS) toxicity and cardiovascular collapse is less for bupivacaine than for lidocaine (6,13–15), an observation that may be related to the arrhythmogenic potential of bupivacaine.

Recently a new amino-amide local anesthetic agent, ropivacaine, has become available. In animal studies, ropivacaine appears equipotent to bupivacaine with regard to sensory anesthesia, but slightly less potent than bupivacaine in terms of motor block-

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ade (16,17). Its physicochemical properties are also similar to those of bupivacaine (17,18).

The current study was designed to evaluate the relative systemic toxicity, arrhythmogenic potential, and mode of death associated with the administration of convulsant and supraconvulsant doses of lidocaine, bupivacaine, and ropivacaine. Unpremedicated and unanesthetized dogs were employed to mimic the clinical situation in which a rapid accidental intravenous (IV) injection of a local anesthetic agent occurs in patients during an attempted regional anesthetic procedure. Premedication with an agent such as diazepam and general anesthesia can alter the toxic profile of local anesthetic drugs. For example, ventricular arrhythmias, which have been reported in humans (1–4) and conscious animals (15), were not seen in anesthetized dogs receiving large IV doses of bupivacaine (12). Resuscitation of animals was not attempted as the protocol was designed to investigate the mode of death and determine the relative margin of safety of these agents. The results obtained indicate that differences in arrhythmogenic potential and margin of safety do exist between these local anesthetics.

Methods

Eighteen adult, male beagle dogs weighing 12.5 ± 3.5 kg (mean ± SEM) were randomly assigned to one of three drug treatment groups. Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals in Research of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (Department of Health and Human Services). Approval of the Animal Care Committee was obtained.

Forty-eight hours before experimentation, animals were anesthetized with IV thiamylal and polyethylene catheters were surgically introduced into the abdominal aorta and inferior vena cava via the femoral vessels utilizing aseptic techniques. A similar catheter was placed in a forelimb vein and a shortened pulmonary artery catheter introducer was inserted in the right external jugular vein for subsequent placement of an internal electrocardiogram (ECG) recording lead. Catheters were flushed with heparinized saline and sealed. Animals were treated with 600,000 U of intramuscular (IM) penicillin G benzanthine suspension and allowed a 48-h recovery period before the first administration of local anesthetic.

The order of drug administration was determined by a random draw so that at the end of the study six animals had received ropivacaine, six received bupivacaine, and six received lidocaine. Each animal received the same local anesthetic on up to 3 consecutive days. Personnel involved with the administration of drug and analysis of data were blinded to the identity of the drug and order of administration. Stock solutions of the local anesthetics were 0.75% ropivacaine HCl, 3.0% lidocaine HCl (Astra Pain Control, Sodertalje, Sweden), and 0.75% bupivacaine HCl (Sensorcaine, Astra Pharmaceutical Products, Inc., Westborough, Mass.). Drug solutions were diluted to required concentrations using sterile water for injection.

On the day of study, animals were weighed and placed in a canvas sling in the standing position. The femoral catheters were flushed with heparinized saline and attached to the appropriate precalibrated transducers for recording blood pressures. Two ECG recordings were made simultaneously, one from a standard limb lead II and the other from a bipolar electrode catheter. The bipolar catheter was passed through the introducer in the jugular vein and advanced slowly toward the heart until an optimal ECG recording was observed. Respiratory rate was monitored using a chest plethysmograph. Measurements were made from recordings on a polygraph (model 7, Grass Instrument Co., Quincy, Mass.) at various time intervals during each experiment.

On the first experimental day the animals received an IV infusion of either bupivacaine (2.0 $mg \cdot kg^{-1} \cdot min^{-1}$), ropivacaine (2.0 $mg \cdot kg^{-1} \cdot min^{-1}$), or lidocaine (8.0 $mg \cdot kg^{-1} \cdot min^{-1}$). Infusion rates were based on rates utilized in similar studies in sheep (6,7). Infusions were administered by a syringe infusion pump, calibrated to deliver 4.0 mL/min, until overt seizure activity was observed, at which time the infusion was terminated. The volume of drug infused was used to calculate the convulsive dose. Twenty-four hours after the first administration of test drug the animals received an intravenous bolus injection given over 30–45 s of two times the convulsive dose calculated from the previous day's infusion. On the third experimental day, the remaining animals received three times the convulsive dose as a bolus injection. These injections were administered to determine the margin of safety between a convulsive dose of drug and a cardiotoxic/lethal dose.

Animals that developed continual seizure activity for 15 min were given an IV injection of 4.0 mg/kg of thiamylal. This was done for two reasons. First, based on previous studies, it was believed that any sudden onset of severe arrhythmias or death would occur within the first 15 min after the injection of test drug and there was no reason to prolong seizure activity (15). Although such a duration of seizure activity should not occur in a clinical setting, the possibility of the occurrence of arrhythmias over this time period could be investigated without the interference of drug interactions. Second, this procedure would provide information regarding the ability of barbiturates to terminate local anesthetic-induced seizures. Animals were observed for at least 30 min after the cessation of seizures.

At regular intervals throughout the course of each experiment, arterial blood samples were withdrawn for determination of pH, Pa_{O_2}, Pa_{CO_2}, and drug concentration determinations. Venous blood hematocrit was also measured. Blood samples for drug concentration analysis were centrifuged to obtain plasma, which was stored at −20°C until required for analysis. Determination of local anesthetic concentrations was performed by Astra Pain Control utilizing gas chromatographic methods. Concentrations are expressed as micrograms of drug base per milliliter of plasma. Additionally, arterial blood pressure, ECG, and respiratory rate were recorded. From the recorded data, heart (HR) and respiratory rate, P-R, QRS, and QT intervals of the ECG, and mean arterial blood pressure (MABP) were determined. The ECG interval measurements were made from the lead II ECG recording with the strip chart speed set at 100 mm/s. Data are expressed as mean ± SEM. Predrug control data consist of the mean value of four predrug measurements in each of the six dogs in each group. All other mean data consist of six values unless noted otherwise. Statistical analyses were performed using analysis of variance, and Student's *t*-tests for paired and unpaired data where appropriate. A Fisher exact probability test was used to compare incidence of death and arrhythmias between groups. Statistical significance was attained at $P \leq 0.05$.

Results

Infusion Studies

The mean dose to cause seizures in the bupivacaine-treated animals was 4.31 ± 0.36 mg/kg, compared with 4.88 ± 0.47 mg/kg in the ropivacaine group and 20.8 ± 4.0 mg/kg in the lidocaine group (Table 1). There was no significant difference between the convulsive doses of bupivacaine and ropivacaine. However, both agents produced convulsions at doses significantly lower than did lidocaine ($P < 0.01$). Although the duration of seizure activity was longest in the bupivacaine-treated animals (307 ± 39 s) as compared with the lidocaine group (200 ± 58 s) and the ropivacaine group (190 ± 53 s), no statistically significant difference existed among the groups (n = 6 in each group).

Table 1. Mean Onset and Duration of Seizures After Intravenous Infusion of Local Anesthetics

	Dose (mg/kg)	Onset (s)	Duration (s)
Bupivacaine	4.31 ± 0.36	130 ± 10	307 ± 39
Ropivacaine	4.88 ± 0.47	149 ± 14	190 ± 53
Lidocaine	20.8 ± 4.0[a]	150 ± 31	200 ± 58

Values given as mean ± SEM (n = 6). Onset of seizures is from start of infusion; duration of seizures is from onset.

[a] $P < 0.01$ compared with bupivacaine and ropivacaine.

Predrug baseline values in this study were not significantly different among the groups (Table 2). Heart rates in both the bupivacaine- and ropivacaine-treated dogs did not change significantly after starting the infusion, whereas in lidocaine-treated animals there was an initial significant increase in HR. Significant increases in HR were observed in all treatment groups at the start of seizure activity. Increases in HR at this time ranged from 29% in the bupivacaine group (from 117 ± 4 to 151 ± 10 beats/min) to 47% and 53% in the lidocaine-treated (from 121 ± 3 to 178 ± 15 beats/min) and ropivacaine-treated (from 122 ± 4 to 187 ± 17 beats/min) animals. There was no significant difference in the increase observed between the three groups. Within 5 min of the cessation of seizure activity, HRs had returned to predrug control values.

No significant change in the P-R interval occurred in the ropivacaine-treated animals, whereas a significant prolongation of the P-R interval was observed in the bupivacaine group (from 86 ± 2 to 114 ± 3 ms) at the time seizures began. The lidocaine treatment group showed a significant decrease in the P-R interval (from 97 ± 2 to 90 ± 3 ms). There were no significant increases in the QRS interval observed in any of the groups at the time seizures began. The QT interval shortened in all treatment groups at the time seizures began, but this reached statistical significance only in the lidocaine group (from 200 ± 3 to 178 ± 6 ms). There was, however, no difference in the degree of decrease between the three groups.

Arrhythmias observed during the infusion studies consisted of an occasional rare incidence of premature ventricular contractions observed in some animals during the predrug control period. These were probably due to mechanical stimulation from the internal ECG electrode and were considered benign. One animal in the ropivacaine treatment group developed a 15-s burst of ventricular tachycardia 1 min

Table 2. Summary of Results of Intravenous Infusions of the Convulsive Dose of Bupivacaine, Ropivacaine, and Lidocaine

		Bupivacaine	Ropivacaine	Lidocaine
HR	C	117 ± 4	122 ± 4	121 ± 3
(beats/min)	SS	151 ± 10^a	187 ± 17^a	178 ± 15^a
	5ES	103 ± 7	102 ± 6	118 ± 6
P-R	C	96 ± 2	99 ± 4	97 ± 2
(ms)	SS	114 ± 3^a	105 ± 3 (4)	90 ± 3^a (5)
	5ES	108 ± 5	104 ± 8	95 ± 2
QRS	C	59 ± 1	62 ± 1	59 ± 1
(ms)	SS	69 ± 4	64 ± 2 (4)	58 ± 2 (5)
	5ES	63 ± 2	63 ± 2	60 ± 0
QT	C	207 ± 4	202 ± 3	200 ± 3
(ms)	SS	195 ± 3	180 ± 7 (4)	178 ± 6^a (5)
	5ES	213 ± 4	207 ± 6	196 ± 5
MAPB	C	130 ± 2	129 ± 2	132 ± 2
(mm Hg)	SS	188 ± 17^a	195 ± 18^a	164 ± 16
	5ES	128 ± 7	137 ± 5	134 ± 6
pH	C	7.44 ± 0.01	7.46 ± 0.00	7.45 ± 0.01
	3SS/1SS/SS	7.40 ± 0.02^a (5)	7.33 ± 0.02^a	7.43 ± 0.02
	5ES	7.41 ± 0.01	7.39 ± 0.02	7.39 ± 0.01
Pa_{O_2}	C	94 ± 2	92 ± 2	93 ± 2
(mm Hg)	SS	90 ± 9	61 ± 8^a	96 ± 10
	5ES	99 ± 3	94 ± 4	97 ± 5
Pa_{CO_2}	C	32 ± 1	30 ± 1	30 ± 1
(mm Hg)	SS	27 ± 3	35 ± 2^a	30 ± 2
	5ES	26 ± 2	26 ± 3	29 ± 1
Hematocrit	C	44 ± 2	42 ± 2	43 ± 1
(vol %)	ES	54 ± 1^a	52 ± 2^a	49 ± 1^a
	5ES	50 ± 1	48 ± 1	47 ± 1

Values are mean ± SEM.

C, control ($n = 24$) except for blood gases, pH, Na, and K which have an n of 12. All other values have an $n = 6$ unless noted otherwise parenthetically. SS, 1SS, 3SS, start of seizures, 1 and 3 min after seizures have started, respectively. 5ES, 5 min after seizures have stopped.

$^a P < 0.05$ from mean control, paired t-test.

after the onset of seizures that then spontaneously reverted to normal sinus rhythm.

A statistically significant increase in MABP was observed in the bupivacaine (from 130 ± 2 to 188 ± 17 mm Hg) and ropivacaine (from 129 ± 2 to 195 ± 18 mm Hg) groups during the first 3 min of seizures (Table 2). The increase seen in the lidocaine group at this time was not statistically significant (from 132 ± 2 to 164 ± 16 mm Hg). These increases in MABP were not significantly different among the groups. Within 5 min after cessation of convulsive activity, MABP had returned to near predrug baseline values.

Significant decreases in pH occurred at 1 min after the onset of seizures in the ropivacaine group (from 7.46 ± 0.00 to 7.33 ± 0.02) and 3 min after the onset of seizures in the bupivacaine group (from 7.44 ± 0.01 to 7.40 ± 0.02), whereas the lidocaine treatment group showed decreases in pH (from 7.45 ± 0.01 to 7.43 ± 0.02) that were not statistically significant (Table 2). Minimum mean pH values for the three groups ranged from 7.31 to 7.38. The ropivacaine group developed a significantly greater decrease in pH (2.0% ± 0.1%) than did the bupivacaine group (0.9% ± 0.3%). Within 3 min of cessation of seizures, pH had returned to predrug control values.

The ropivacaine group had a transient, but significant decrease in Pa_{O_2} of 34% (from 92 ± 2 to 61 ± 8 mm Hg) below predrug baseline values at the onset of seizure activity (Table 2). No significant changes in Pa_{O_2} were observed during seizure activity in the bupivacaine or lidocaine groups. There was a return to control values or a slight increase in Pa_{O_2} observed in all groups at the time seizures ceased.

The ropivacaine-treated group also had demonstrated a significant 17% increase in Pa_{CO_2} (from 30 ± 1 to 35 ± 2 mm Hg) at the time convulsions began. In bupivacaine-treated animals Pa_{CO_2} decreased 16% (from 32 ± 1 to 27 ± 3 mm Hg) at the time seizures began, a change that reached significance after 3 min of convulsive activity, whereas the lidocaine-treated

Table 3. Arterial Plasma Drug Concentrations at the Start and End of Seizure Activity After Intravenous Infusion

	Concentration (μg drug base/mL)	
	Start seizures	End seizures
Bupivacaine	18.0 ± 2.7	3.22 ± 0.31
Ropivacaine	11.4 ± 0.9[a]	3.97 ± 0.21
Lidocaine	47.2 ± 5.4[b]	9.81 ± 1.20[b]

Values given as mean ± SEM (n = 6).
[a] $P < 0.05$ compared with bupivacaine.
[b] $P < 0.05$ compared with bupivacaine and ropivacaine.

animals showed no change in $Paco_2$ (from 30 ± 1 to 30 ± 2 mm Hg). Within 3 min after seizures stopped, $Paco_2$ values in all three groups had returned to predrug control values. Venous hematocrit was significantly increased in all treatment groups by the time seizures ended. Within 5 min of the cessation of seizures, hematocrit values had returned toward normal.

Lidocaine plasma concentrations were greater than those of bupivacaine and ropivacaine at both the start and end of seizures (Table 3). The mean arterial ropivacaine plasma concentration at the onset of seizures was significantly less than for bupivacaine but there was no difference in concentrations at the end of seizures. In general, the concentration versus time profiles were very similar for both bupivacaine and ropivacaine.

Bolus Injection Studies

Table 4 presents a summary of the results of the IV bolus injection of two times the convulsant dose. Predrug control values on the day of the two-times convulsive dose bolus injections were similar to those observed on the day of the infusion study. Convulsions were observed in all animals (n = 6 in each group) receiving two times the convulsive dose. One animal in the lidocaine group and one in the ropivacaine group spontaneously ceased convulsive activity at 514 and 805 s after the start of seizures.

There were five deaths in the bupivacaine group at two times the convulsive dose. The mean time of death was 218 ± 50 s after the start of injection. Four of these animals developed ventricular arrhythmias consisting of premature ventricular contractions, atrioventricular dissociation, ventricular tachycardia, or ventricular fibrillation, alone or in combination. The sole survivor in this group also had ventricular arrhythmias. Four of the animals succumbed to hypotension, respiratory arrest, and cardiovascular collapse. One dog developed primary ventricular fibrillation 84 s after the start of drug administration.

Severe hypotension and respiratory arrest, and ultimately asystole, developed in two animals in the lidocaine group. There were no ventricular arrhythmias in this group. Ventricular arrhythmias developed in two dogs given ropivacaine. One dog showed an 8-s burst of ventricular tachycardia ~30 s after seizures began. This animal had occasional premature ventricular contractions for an additional 60 s at which time respiratory arrest occurred. Blood pressure rapidly dropped and finally, 3 min later, the ECG showed an agonal rhythm of ventricular fibrillation. The second dog had developed atrioventricular dissociation and ~3 min of multifocal ventricular rhythm that spontaneously terminated. This dog, as well as the other seven animals with prolonged seizures, was treated with 4 mg/kg IV thiamylal after 15 min of seizure activity. This promptly caused overt seizure activity to cease, sedated the animal, and allowed a quiet recovery period. Analysis of the incidence of death at this dosage level indicated that bupivacaine (83%) was significantly more lethal than ropivacaine (17%) but not different from lidocaine (33%). The incidence of arrhythmias in the bupivacaine group (83%) was also significantly higher than the ropivacaine group (33%) and lidocaine group (0%).

Peak plasma concentrations (Table 5) were similar for both ropivacaine and bupivacaine, and no differences in plasma drug concentrations existed between animals that survived this dose and those that did not. The two animals in the lidocaine group that died had the highest doses of drug and the highest plasma concentrations recorded in this study (Table 5). Increases in hematocrit were again observed in all treatment groups.

The survivors of the bolus injection of two times the convulsive dose were given three times the convulsive dose 24 h later. The one remaining animal in the bupivacaine group developed seizures 18 s after the start of the injection. Ventricular arrhythmias consisting of premature ventricular contractions and paroxysmal ventricular tachycardia developed. These began 15 s after completing the administration of drug. Arterial blood pressure decreased gradually and continuously after the injection had been completed. Respiratory movements stopped 30 s later. The ECG continued to show paroxysms of ventricular tachycardia but pulse pressure was nonexistent.

Seizures developed in the four animals in the lidocaine group 30.5 ± 3.4 s after the start of the injection (mean injection time was 38.0 ± 1.0 s). Three animals died because of hypotension and respiratory arrest leading to circulatory collapse and finally asystole 66 ± 8 s after the injection of drug.

Table 4. Summary of Results of Intravenous Bolus Injection of Two Times the Convulsive Dose of Bupivacaine, Ropivacaine, and Lidocaine

		Bupivacaine	Ropivacaine	Lidocaine
↑ HR (beats/min)	C	131 ± 5	130 ± 7	133 ± 5
	Δ	170 ± 10	186 ± 12 (4)	173 ± 16 (5)
↑ P-R (ms)	C	95 ± 2	96 ± 3	95 ± 2
	Δ	112 ± 7 (3)	112 ± 9 (3)	111 ± 7 (3)
↑ QRS (ms)	C	62 ± 1	61 ± 1	60 ± 1
	Δ	73 (2)	70 ± 0 (4)	63 ± 3 (3)
↓ QT (ms)	C	204 ± 3	201 ± 4	193 ± 3
	Δ	—	167 ± 7 (5)	154 ± 5 (4)
↓ MABP (mm Hg)	C	130 ± 3	120 ± 3	121 ± 1
	Δ	49 ± 6 (4)	111 ± 10 (3)	84 (2)
↓ pH (U)	C	7.45 ± 0.01	7.44 ± 0.10	7.44 ± 0.00
	Δ	7.24 ± 0.05	7.27 ± 0.04	7.29 ± 0.04
↓ Pa_{O_2} (mm Hg)	C	93 ± 3	93 ± 2	92 ± 2
	Δ	47 ± 7	57 ± 11	57 ± 6 (5)
↑ Pa_{CO_2} (mm Hg)	C	30 ± 1	30 ± 1	29 ± 1
	Δ	47 ± 5	41 ± 4	37 ± 3 (4)
↑ Hematocrit (vol %)	C	39 ± 2	37 ± 2	37 ± 1
	Δ	49 ± 1 (5)	51 ± 2	47 ± 2 (3)

Values given as mean ± SEM.

C, predrug control ($n = 24$); Δ, maximum change ($n = 6$ unless otherwise noted in parentheses); ↓, values are maximum decrease; ↑, values are maximum increase.

Table 5. Start Seizure Plasma Drug Concentration Resulting from the Intravenous Bolus Injection of Two Times the Convulsant Dose

	All animals (n = 6)		Nonsurvivors		
	Dose (mg/kg)	Plasma concentration (μg/mL)	n	Dose (mg/kg)	Plasma concentratio (μg/mL)
Bupivacaine	8.60 ± 0.67	67.4 ± 12.2	5	8.24 ± 0.71	70.1 ± 14.6
Ropivacaine	9.75 ± 0.94	68.3 ± 7.7	1	9.33	72.4
Lidocaine	41.7 ± 8.0	271 ± 64.0	2	66.6	469

Values given as mean ± SEM.

One dog survived this dose of lidocaine. No arrhythmias were noted in the lidocaine-treated animals. There was no apparent difference between the peak lidocaine concentration in the animal that survived (239 μg/mL) and those that did not (range 196–326 μg/mL).

Seizures developed in the five surviving dogs given ropivacaine at 22 ± 2 s after the injection was started (mean injection time was 35.6 ± 1.1 s). Four of the five animals died because of hypotension and respiratory arrest leading to cardiac arrest 67 ± 16 s after ending the injection. One dog survived this dose of ropivacaine. Ventricular arrhythmias were observed in animals at this dosage level of ropivacaine. The arrhythmias consisted of atrioventricular dissociation, multifocal ventricular beats, and paroxysmal ventricular tachycardia. One dog demonstrated ventricular tachycardia that degenerated to terminal ventricular fibrillation after respiratory movements had ceased. The surviving animal in the ropivacaine group had the lowest peak plasma concentration of the five animals (53.7 μg/mL compared with the range of 63.0–82.5 μg/mL in nonsurvivors).

Discussion

Ropivacaine is a new amino-amide local anesthetic agent that is chemically related to bupivacaine (17,18). The physicochemical properties and local anesthetic profile of ropivacaine are similar to those of bupivacaine. In vitro isolated nerve studies and in vivo studies in various species indicate that ropivacaine is equipotent to bupivacaine in terms of sensory analgesia and slightly less potent in terms of motor blockade (16–18).

Previous studies in laboratory animals have shown that the CNS toxicity of local anesthetics is proportional to their anesthetic potency. However, several studies have indicated that bupivacaine and etidocaine are relatively more cardiotoxic than agents such as lidocaine (5–12,19).

The total doses required to produce seizures for bupivacaine and lidocaine in this study are comparable to those previously reported in dogs receiving increasing serial doses (14). They are also similar to the doses reported in cats (5), monkeys (20), and sheep (7,8). The results of the current study indicate that bupivacaine and ropivacaine are approximately four to five times more potent than lidocaine in terms of CNS toxicity. There was no significant difference between the convulsive doses of bupivacaine and ropivacaine. The current study also supports the contention that the relative CNS toxicity of these three agents is proportional to their local anesthetic potency. The mean duration of seizure activity in the bupivacaine-treated group was longer than that of the other two groups, although the differences were not significant. This may be due to the relatively small number of animals in each group. Intravenous lidocaine and ropivacaine have been reported to be cleared somewhat more rapidly than bupivacaine, which may result in a shorter duration of seizure activity (21). The lower plasma concentrations of ropivacaine compared with bupivacaine at the onset of seizures are also probably due to the greater clearance of ropivacaine. During IV infusion or bolus injection of local anesthetics, the peak arterial concentration of drug is probably a poor indicator of the actual toxic plasma concentration as this value is very dependent on both cardiac output and rate of drug input. The better indicator of the threshold toxic plasma concentration is that seen at the end of seizures where no significant difference was seen between bupivacaine data (3.22 ± 0.31 μg/mL) and ropivacaine data (3.97 ± 0.21 μg/mL). Intravenous thiamylal was consistently effective in terminating convulsions in all animals so treated. Unlike bupivacaine and lidocaine, ropivacaine infusion caused a transient decrease in Pa_{O_2} values. The reason for this is unclear. The Pa_{O_2} values returned to normal values by 5 min after the cessation of seizures. Additionally, the reduction in Pa_{O_2} in the ropivacaine group was not different than that observed in the lidocaine or bupivacaine group after the bolus injection of two times the convulsive dose. Venous hematocrit increased in all treatment groups in association with seizure activity. This increase was observed after the infusion studies and after the bolus injection of two times the convulsive dose. A similar increase has been previously reported in dogs (15). It is thought that this increase may be associated with release of blood cells from the dog's spleen during seizures.

Bupivacaine appears to be potentially more cardiotoxic than either lidocaine or ropivacaine. After two times the convulsant dose was administered, 83% of the bupivacaine-treated dogs died, compared with 33% in the lidocaine group and 17% in the ropivacaine group. In addition, 83% of the bupivacaine-treated dogs demonstrated ventricular arrhythmias, compared with 33% in the ropivacaine group and 0% in the lidocaine group. As would be expected with the similar doses of bupivacaine and ropivacaine, the peak plasma drug concentrations were very similar, implying that lower circulating concentrations of bupivacaine than ropivacaine may precipitate cardiovascular collapse. Thus, within 15 min of the administration of two times the convulsive dose, bupivacaine was more arrhythmogenic and more lethal than either lidocaine or ropivacaine. These data are in agreement with recent studies in which bupivacaine, ropivacaine, and lidocaine were administered directly into the coronary arteries of pigs. Ropivacaine was reported to have an ~75% greater margin of safety than bupivacaine. In addition, the arrhythmogenic potential of ropivacaine was less than that of bupivacaine (22).

There also appear to be differences in the mechanisms of local anesthetic-induced lethality. One is the sudden onset of ventricular fibrillation, which was seen in one bupivacaine-treated animal in this study and which has been reported previously in dogs and other species (15). This was not observed in either lidocaine- or ropivacaine-treated animals. Other modes of death consisted of hypotension with or without ventricular arrhythmias. In both of these situations respiratory arrest occurred, followed by further depression of blood pressure and eventually asystole or agonal ventricular rhythm. Lidocaine-treated animals at all dosage levels showed no ventricular arrhythmias. The terminal ECG recording was generally asystole or complete heart block with only P waves being recorded. This is distinctly different than events recorded with either bupivacaine or ropivacaine. The reason for this is unclear but may be related to differences in the direct effects upon myocardial cells (23) or individual portions of the cardiac conduction system. These differences may be important in terms of the clinical treatment of local anesthetic overdosage. Electrical cardioversion is probably required for the treatment of primary ventricular fibrillation. In other cases, therapy should include control of seizures, ventilatory support, and use of vasopressor and antiarrhythmic agents such as bretylium (24,25). Studies examining the treatment and resuscitation of local anesthetic overdose are currently being conducted.

In summary, the results of the current investigation indicate that the new amide local anesthetic agent, ropivacaine, possesses a greater margin of safety than bupivacaine if one compares the dose to cause convulsions and the dose to cause cardiovascular collapse and death. In addition, the arrhythmogenic potential of ropivacaine is less than that of bupivacaine. However, lidocaine was the only agent that was consistently devoid of arrhythmogenic activity.

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References

1. Edde RR, Deutsch S. Cardiac arrest after interscalene brachial-plexus block. Anesth Analg 1977;56:446–7.
2. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285–7.
3. Davis NL, DeJong RH. Successful resuscitation following massive bupivacaine overdose. Anesth Analg 1982;61:62–4.
4. Moore DC, Scurlock JE. Possible role of epinephrine in prevention or correction of myocardial depression associated with bupivacaine. Anesth Analg 1983;62:450–3.
5. DeJong RH, Ronfeld RA, De Rosa RA. Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 1982;61:3–9.
6. Morishima HO, Pedersen H, Finster M, et al. Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology 1985;63:134–9.
7. Morishima HO, Pedersen H, Finster M, et al. Toxicity of lidocaine in adult, newborn, and fetal sheep. Anesthesiology 1981;55:57–61.
8. Tanz RD, Heskett T, Loehning RW, Fairfax CA. Comparative cardiotoxicity of bupivacaine and lidocaine in the isolated perfused mammalian heart. Anesth Analg 1984;63:549–56.
9. Kotelko DM, Shnider SM, Dailey PA, et al. Bupivacaine-induced cardiac arrhythmias in sheep. Anesthesiology 1984; 60:10–8.
10. Clarkson CW, Hondeghem LM. Mechanism for bupivacain depression of cardiac conduction: fast block of sodium channels during the action potential with slow recovery from bloc during diastole. Anesthesiology 1985;62:396–405.
11. Nath S, Haggmark S, Johansson G, Reiz S. Differential depressant and electrophysiologic cardiotoxicity of local anesthetics an experimental study with special reference to lidocaine an bupivacaine. Anesth Analg 1986;65:1263–70.
12. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG. Acut cardiovascular toxicity of intravenous amide local anesthetic in anesthetized ventilated dogs. Anesth Analg 1982;61:317–22
13. DeJong RH, Bonin JD. Deaths from local anesthetic induce convulsions in mice. Anesth Analg 1980;59:401–5.
14. Liu PL, Feldman HS, Giasi R, Patterson MK, Covino BG Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine and tetracaine in awake dog following rapid intravenous administration. Anesth Analg 1983;62:375–9.
15. Sage DJ, Feldman HS, Arthur GR, Doucette AM, Norway SB Covino BG. The cardiovascular effects of convulsant doses o lidocaine and bupivacaine in the conscious dog. Reg Anaest 1985;10:175–83.
16. Akerman B, Hellberg IB, Trossvik C. Primary evaluation of th local anaesthetic properties of the primary amino amide agen ropivacaine (LEA-103). Acta Anaesthesiol Scand 1988;32:571–8
17. Feldman HS, Covino BG. Comparative motor-blocking effect of bupivacaine and ropivacaine, a new amino amide loca anesthetic in the rat and dog. Anesth Analg 1988;67:1047–52.
18. Rosenberg PH, Heinonen E. Differential sensitivity of A and nerve fibres to long-acting amide local anaesthetics. Br Anaesth 1983;55:163–7.
19. Feldman HS, Covino BM, Sage DJ. Direct chronotropic an inotropic effects of local anesthetic agents in isolated guine pig atria. Reg Anaesth 1982;7:149–56.
20. Munson ES, Tucker WK, Ausinsch B, Malagodi MH. Etidocaine, bupivacaine and lidocaine seizure threshold in monkeys. Anesthesiology 1975;42:471–8.
21. Arthur GR, Feldman HS, Covino BG. Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide loca anesthetic. Anesth Analg 1988;67:1053–8.
22. Reiz S, Haggmark G, Johannson G, Nath S. Cardiotoxicity o ropivacaine—a new amide local anaesthetic agent. Acta Anaesthesiol Scand 1989;33:93–8.
23. Moller RA, Covino BG. Cardiac electrophysiologic effects o lidocaine and bupivacaine. Anesth Analg 1988;67:107–14.
24. Kasten GW, Martin ST. Successful cardiovascular resuscitatio after massive intravenous bupivacaine overdosage in anesthetized dogs. Anesth Analg 1985;64:491–7.
25. Kasten GW, Martin ST. Bupivacaine cardiovascular toxicity comparison of treatment with bretylium and lidocaine. Anest Analg 1985;64:911–6.

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What Is the Safest Endotracheal Tube for Nd-YAG Laser Surgery?—A Comparative Study

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SOSIS MB. What is the safest endotracheal tube for Nd-YAG laser surgery?—A comparative study. Anesth Analg 1989;69:802–4.

To determine whether a safe endotracheal tube for Nd-YAG surgery could be found, an Nd-YAG laser operating at 50 W was directed at six different endotracheal tubes that had 5 L/min of oxygen flowing through them. A plain Rusch red rubber endotracheal tube, a Bivona Fome-cuff laser endotracheal tube, a stainless steel Mallinckrodt Laser-Flex endotracheal tube, and a Xomed Laser-shield endotracheal tube were all ignited and perforated by the laser within 12 s. The combustion of the Mallinckrodt endotracheal tube can be explained by the high energy density of the laser that, in rapidly heating the metal, was able to cause its combustion in 100% oxygen. Red rubber endotracheal tubes wrapped with 3M No. 425 or Venture copper foil tape were unaffected by 1 min of exposure to the laser beam. They are recommended for clinical use.

Key Words: EQUIPMENT, TRACHEAL TUBES—lasers. SURGERY, LASER—tracheal tubes.

The neodymium-yttrium-aluminum-garnet (Nd-YAG) laser is being increasingly utilized for airway surgery. It has excellent hemostatic properties and a large depth of penetration (1). The Nd-YAG laser is especially useful in the treatment of obstructing tracheobronchial tumors as, unlike the carbon dioxide (CO_2) laser, the laser beam can be conducted via a fiber-optic bundle. A study by Geffin et al. (2) on endotracheal tube flammability on exposure to an Nd-YAG laser beam concluded that all the endotracheal tubes tested were vulnerable to the effects of this laser when the beam was directed at the shafts of the endotracheal tubes if 50 W of power in the continuous mode was used. Life-endangering fires may result from such laser-induced combustion of an endotracheal tube. For example, Casey et al. (3) have published a report noting combustion of a polyvinylchloride endotracheal tube and fiberoptic bronchoscope during Nd-YAG airway surgery. Burns were subsequently noted in the patient's airway.

The present study was initiated to determine the safest endotracheal tube for use with the Nd-YAG laser with the laser operating at a high power level and with 100% oxygen (O_2) flowing through it. The foil wrapping techniques that were found suitable for use with the CO_2 (4) and Nd-YAG (5) lasers in previous studies and special endotracheal tubes designed for laser use were compared.

Materials and Methods

A LaserSonics (Santa Clara, Calif.) model 1700 combined CO_2/Nd-YAG laser in the Nd-YAG mode and a Zeiss operating microscope with a 400-mm lens and "joy-stick" micromanipulator were used in this study. It was our intention to test the endotracheal tubes under stringent conditions (2) to determine which endotracheal tube was the safest. The laser's output was set to 50 W in the continuous mode of operation with a beam diameter of 0.68 mm. Power settings up to 90 W have been described in clinical practice; however, durations of less than 2 s are commonly used. Thus the amount of energy impinging on the endotracheal tubes in this study was considerably greater than in usual clinical practice. The laser's emission was continued for 1 min or until combustion occurred. The beam was directed perpendicularly onto the shafts of three different red rubber (RR) endotracheal tubes, as they have been shown to be vulnerable to the Nd-YAG laser (2). The endotracheal tubes had 5 L/min of O_2 flowing

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through them so that ignition of an endotracheal tube would be clearly seen. The tubes rested on wet towels and were surrounded by air. The endotracheal tubes studied were as follows: (1) a Rusch (F.R.G.) RR tube; (2) an RR tube wrapped with 3M (St. Paul, Minn.) No. 425 aluminum foil tape (4,5); (3) an RR tube wrapped with 1-mil copper foil tape manufactured by the Venture Tape Corp. of Rockland, Mass. (4,5); (4) a Bivona (Gary, Ind.) Fome-Cuf 6.0-mm-ID laser endotracheal tube; (5) a Mallinckrodt (St. Louis, Mo.) Laser-Flex stainless steel 6.0-mm-ID tracheal tube; and (6) a Xomed (Jacksonville, Fla.) Laser-shield 6-mm-ID endotracheal tube.

Tubes 1 and 4 had the laser directed at an unmarked portion of the tube. Tubes 2 and 3 had the metallic foils wrapped in an overlapping spiral manner starting just above the cuffed end of the tube with a single piece of tape.

Results

Within 2 s of the start of the laser's emission, the bare RR tube was penetrated. A blowtorch fire occurred at 13 s, but the tube remained in one piece and the combustion stopped when the O_2 source was interrupted. Smoke was seen at the site of laser impact within 1 s with the Bivona laser tube. A fire occurred by 12 s, but the tube remained in one piece and no blowtorch fire occurred. This fire was also terminated by stopping the O_2 flow.

A blowtorch fire occurred after 10 s of laser contact with the Mallinckrodt Laser Flex tube. Interrupting the flow of O_2 ended the fire. The tube remained in one piece. Flames appeared within 1 s at the point of the laser beam's impact on the Xomed tube. The tube broke into several pieces with considerable flaming by 12 s. Even after stopping the laser and turning off the O_2 supply, this fire was very difficult to extinguish.

The RR endotracheal tubes wrapped with the 3M No. 425 aluminum tape and the Venture copper foil tapes were unaffected by 1 min of exposure to the Nd-YAG laser beam. Three more such laser tests of each had the same result.

Discussion

The use of an Nd-YAG or CO_2 laser for operations in the airway usually places the surgeon and anesthesiologist in competition. The high energy density delivered by the laser in proximity to combustible materials such as an endotracheal tube conducting a gas mixture enriched in O_2 has caused catastrophic airway fires resulting in serious airway burns. For example, a report has been published of a polyvinylchloride endotracheal tube and fiber-optic bronchoscope that ignited during Nd-YAG endoscopic resection of a tracheal stenosis. This produced an ulcerated burn to the patient's airway near the carina (3).

The Nd-YAG laser emits radiation at 1064 nm in the near infrared region and is thus invisible (1). The beam has better hemostatic properties and penetrates more deeply than the CO_2 laser beams and can be conducted through a fiber-optic bundle. It has been useful for endoscopic resection of obstructing lesions of the major airways in patients that are usually given general anesthesia (6).

Geffin et al. (2) reported on the combustibility of clear polyvinylchloride, RR, and silicone endotracheal tubes with the Nd-YAG laser at power levels up to 50 W with a spot diameter of 2 mm. They found that all the tubes tested were vulnerable to the Nd-YAG laser at 50 W in the continuous mode. The clear PVC tubes were, however, more resistant to the Nd-YAG laser than the rubber or silicone tubes. However, on directing the laser onto the black printing on the PVC tubes, combustion was facilitated. On the subject of foil wrapping to protect combustible endotracheal tubes, they state: "Although reflective aluminum tape was effective in protecting tubes from exposure to the CO_2 laser, the tape offered no protection from the Nd-YAG laser." However, Geffin et al. only evaluated one type of aluminum tape (Radio Shack 49-502).

Our results (5) using Venture copper foil or 3M No. 425 aluminum foil tapes demonstrate that they provide the only effective protection of combustible endotracheal tubes from the Nd-YAG laser operating at high power found to date. Because of the flammable nature of the adhesive on the Venture copper foil, the 3M No. 425 tape is preferred (5). This technique is simple and inexpensive. We have gas-sterilized RR endotracheal tubes wrapped with these tapes without affecting their flammability. Our findings showing that the RR and Xomed Laser-shield tubes were quickly penetrated by the Nd-YAG laser are consistent with those of Geffin et al. (2). None of the special endotracheal tubes manufactured for use with the CO_2 laser that were evaluated in this study could withstand the impact of the Nd-YAG laser. These endotracheal tubes are not, however, recommended by their manufacturers for use with the Nd-YAG laser.

The combustion of the Mallinckrodt Laser-Flex endotracheal tube after 6 s of laser impact is remarkable considering its shaft is fabricated from stainless steel. The high energy density and coherence of the laser resulted in rapid melting of the steel. Once perforation occurred, the presence of 100% O_2 led to rapid oxidation of the metal and a fire.

The cuffs of the foil-wrapped endotracheal tubes are still vulnerable to the effects of the laser. They should be protected by filling them with saline (7) to which a small amount of dye such as methylene blue has been added, and by packing them off with wet pledgets that are kept moist. The dye serves as a sign of cuff perforation. The minimum acceptable concentration of O_2 diluted with helium or nitrogen should be used during laser airway surgery.

The wrapped endotracheal tubes evaluated in this study are still subject to indirect combustion (8) from sparks or a high temperature in proximity to the tube. Furthermore, a combustible endotracheal tube wrapped with foil tape may not provide adequate protection for fiber-optic bronchoscopic Nd-YAG laser surgery, as the internal aspect of the tube is unprotected. Dumon et al. (9) recommend the use of a rigid bronchoscope instead of an endotracheal tube for Nd-YAG laser surgery of the tracheobronchial tree. Rontal et al. (10) suggest that when peripheral lung lesions are to be treated, a fiber-optic bronchoscope should be passed through a rigid bronchoscope rather than through an endotracheal tube.

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References

1. Van der Spek AFL, Spargo PM, Norton ML. The physics of lasers and implications for their use during airway surgery. Br J Anaesth 1988;60:709–29.
2. Geffin B, Shapshay SM, Bellack GS, Hobin K, Stezer SE. Flammability of endotracheal tubes during Nd-YAG laser application in the airway. Anesthesiology 1986;65:511–5.
3. Casey KR, Fairfax WR, Smith SJ, Dixon JA. Intratracheal fire ignited by the Nd-YAG laser during treatment of tracheal stenosis. Chest 1983;84:295–6.
4. Sosis MB. Evaluation of five metallic tapes for protection of endotracheal tubes during CO_2 laser surgery. Anesth Analg 1989;68:392–3.
5. Sosis M, Dillon F, Heller S. A comparison of metallic tapes for protection of endotracheal tubes during Nd-YAG laser surgery. Anesth Analg 1989;68:S270.
6. Dumon JF, Reboud E, Garbe L, Aucomte F, Meric B. Treatment of tracheobronchial lesions by laser photoresection. Chest 1982;81:278–84.
7. LeJeune FE Jr, Guice C, Letard F, Marice H. Heat sink protection against lasering endotracheal cuffs. Ann Otol Rhinol Laryngol 1982;91:606–7.
8. Hirshman CA, Smith J. Indirect ignition of the endotracheal tube during carbon dioxide laser surgery. Arch Otolaryngol Head & Neck Surg 1980;106:639–41.
9. Dumon JF, Shapshay S, Bourcereau J, et al. Principles for safety in application of neodymium-YAG laser bronchology. Chest 1984;86:163–8.
10. Rontal M, Rontal E, Wenokor ME, Elson L. Anesthetic management for tracheobronchial laser surgery. Ann Otol Rhinol Laryngol 1986;95:556–60.

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Review Article

Role of Pulmonary Surfactant in the Development and Treatment of Adult Respiratory Distress Syndrome

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Key Words: LUNG, ADULT RESPIRATORY DISTRESS SYNDROME.

The adult respiratory distress syndrome (ARDS) was described for the first time by Ashbaugh et al. (1) in 1967. Presently, ARDS is a well-known cause of acute respiratory failure in both adults and children after a variety of pulmonary or systemic insults including sepsis, shock, pneumonia, trauma, drug overdose, liquid aspiration, metabolic disorders, hematologic disorders, radiation pneumonitis, smoke inhalation, oxidant injury, and many others (2,3). Regardless of the etiology of the lung injury, ARDS is characterized by five hallmarks: (a) severe arterial hypoxemia refractory to oxygen therapy, (b) increased intrapulmonary shunting, (c) decreased lung compliance, (d) decreased lung volumes, and (e) the absence of indicators of left ventricular failure ([pulmonary wedge pressure <18 mm Hg]; [1–6]).

In adults, the incidence of ARDS in the United States is now estimated at 150,000 cases per year, and the associated mortality rate for full-blown ARDS has been reported at levels as high as 50%–70% (5). In the pediatric population, the incidence of ARDS has been reported at 8.5–10.4 cases per 1000 admissions to pediatric intensive care units with an associated mortality of around 59% (7–9).

The pathophysiology and clinical management o ARDS has been the subject of a number of excellen reviews (2–6). The main objective of clinical management is the maintenance of adequate arterial anc tissue oxygenation and treatment of the precipitatin disorder. The former is achieved by mechanical ventilation with positive end-expiratory pressure anc supplemental oxygen. This type of supportive treatment may not always be effective. In addition, prolonged mechanical ventilation with high pressure and oxygen is associated with increased incidence o barotrauma, pneumothorax (2), and oxygen toxicit (10). Furthermore, the efficacies of various pharmacologic treatments, such as corticosteroids and heparin, are controversial at best (2). For these reasons there is always a search for ways to improve th clinical management of patients with ARDS.

During the last few years, a number of investigators have shown that animals with ARDS-type lun injuries have compromised surfactant function anc that administration of exogenous surfactant mitigates, at least temporarily, the arterial hypoxemi and abnormal lung mechanics and improves surviva (11–16). (Animal models exhibit most but not all th hallmarks of clinical ARDS. For this reason we refe to experimentally induced lung injury as "ARDS type.") Surfactant replacement has been used effectively for the management of neonatal respirator distress syndrome, a disease characterized by primary surfactant deficiency (17–22). A few preliminar reports indicate that it also has potential therapeuti value in patients with ARDS (23,24). A number o clinical studies assessing the efficacy of exogenou surfactant replacement in the outcome of ARDS ar currently either in progress or in the planning stages

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The purpose of this article is twofold: first, we will critically review the existing literature for evidence of surfactant dysfunction in both patients with ARDS and various animal models with experimentally induced lung injury that mimics the clinical manifestations of ARDS. Second, we will assess the efficacy of surfactant replacement in modifying ARDS and ARDS-type injuries and discuss the problems and limitations of this type of treatment. However, before proceeding with a discussion of the pulmonary surfactant system in lung disease, we will review the physiologic, biophysical, and biochemical properties of the pulmonary surfactant system as they apply to the normal lung.

Pulmonary Surfactant System in the Normal Lung

Physiologic Function

Surfactants are molecules that preferentially adsorb at a surface and act to lower interfacial tension as a function of their concentration. This property provides the underlying mechanism by which pulmonary surfactant allows for the variation of surface tension during lung expansion and deflation (Figure 1), and thereby promotes the alveolar stability, minimal work of breathing, and lung inflation uniformity found during normal respiration in a system dominated by surface tension forces (25). Surfactant deficiency causes an increase in the surface tension across the blood-gas barrier leading to atelectasis, increased work of breathing, and decreased lung compliance. In addition, surfactant deficiency may promote the formation of pulmonary edema.

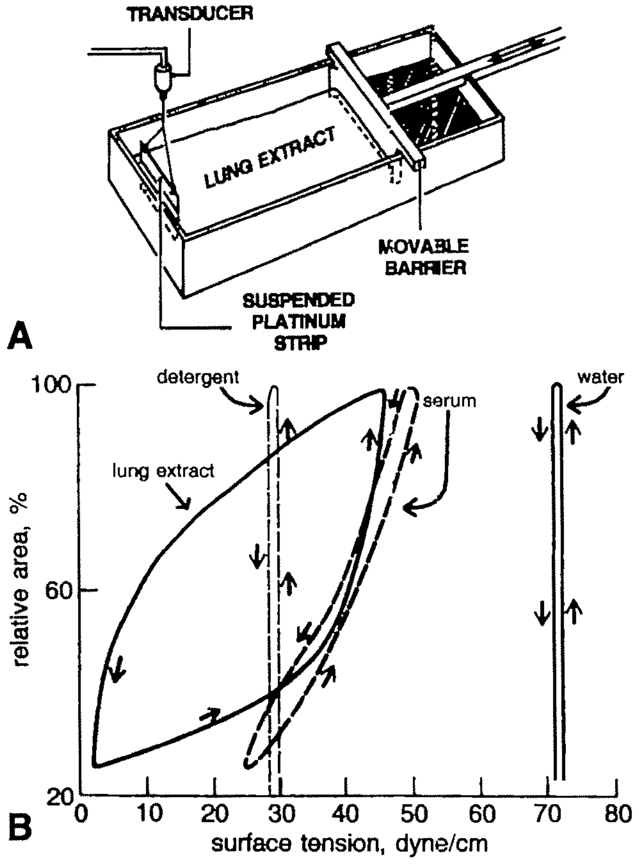

Figure 1. (A) Langmuir–Wilhelmy balance for the measurements of surface tension. Liquid containing a surface active agent is placed in the trough. Surface tension, measured as the force on the platinum strip suspended from a transducer, is continuously recorded as the movable barrier changes the surface area of the air-liquid interface. (B) Surface tension-area relationships of water, water with detergent, serum, and alveolar washings obtained in a Langmuir–Wilhelmy balance. The lung washings show a change in surface tension with area, with different values of surface tensions obtained during compression and expansion (hysteresis). Minimum surface tension is close to zero. The surface tension-area relationship of washings from a surfactant-deficient lung resemble that of serum (small hysteresis and high minimum surface tension.) (Modified from Clements and Tierney, Reference 80, pp. 1567–8.)

Biochemical Composition

Pulmonary surfactant in vivo is a complex mixture of phospholipids and specific apoproteins. As shown in Table 1, phospholipids are the major components of surfactant, accounting for 90% of its composition by weight. Approximately 80% of surfactant phospholipid is phosphatidylcholine, >60% of which contains fully saturated acyl groups (dipalmitoylphosphatidylcholine). This is in sharp contrast to the phosphatidylcholine composition found in cell membranes, including those in the lung (26,27). In addition, phosphatidylglycerol, which makes up <2% of total membrane phospholipids in mammalian cells, has been found to account for as much as 10% of total surfactant phospholipids. However, other phospholipids, such as phosphatidylethanolamine, phosphatidylserine, and sphingomyelin, which are present in significant quantities in mammalian cells, represent only trace components of pulmonary surfactant (27).

Two major groups of surfactant apoproteins have been identified, each representing approximately 1%–2% by weight of the total surfactant composition (27,28). One class of proteins, referred to as SP-A for surfactant apoprotein A (29), appears to represent a single native protein with a highly glycosylated, collagenlike form (28,30). Under reducing conditions, SP-A yields subunits with molecular weights ranging from 26 to 36 kDa, depending on the degree of glycosylation (31–33). Recent studies suggest that SP-A is involved with surfactant recycling and,

Table 1. Biochemical Composition

Component	% Composition (by weight)
Surfactant	
Phospholipids	90
Neutral lipids	6
Proteins	
SP-A (26–36 kDa)	2
SP-B, SP-C (4–18 kDa)	2
Surfactant phospholipid	
Phosphatidylcholine	80
Phosphatidylglycerol	7
Phosphatidylethanolamine	5
Phosphatidylinositol	3
Sphingomyelin	2
Others	3
DPPC/PC (%)	60

DPPC, dipalmitoyl phosphatidylcholine; PC, phosphatidylcholine.

potentially, secretion (34,35). In addition, this protein may also enhance the surface adsorption characteristics of pulmonary surfactant (36).

The second class of surfactant apoproteins is very hydrophobic and extracts with the phospholipids into chloroform (37). These proteins, referred to as SP-B and SP-C, have molecular masses of 18 kDa (8 kDa under reducing conditions) and 4 kDa, respectively. Both are proteolipids and appear to be necessary for optimum surfactant biophysical activity (29,37). Although it is clear that the physiologically relevant surface active properties of lung surfactant are produced as a result of its unique phospholipid and apoprotein composition, detailed structure-function relationships defining the role and necessity of each component of pulmonary surfactant remain to be determined.

Surfactant Metabolism

The majority of evidence to date indicates that the synthesis of surfactant phospholipids and proteins occurs in the microsomal fraction of the alveolar type II pneumocytes (28,38,39). It appears that surfactant phospholipids are synthesized in the endoplasmic reticulum, transported to the Golgi apparatus, and then packaged and stored in the type II pneumocytes' characteristic lamellar inclusion bodies (39,40). Surfactant proteins may follow the same general pathway, but it appears that protein synthesis, posttranslational modification, and movement to lamellar bodies utilizes a method of transport that is different from that used by the phospholipids (28,40–43).

Pulmonary surfactant is secreted from the type II pneumocyte into the alveolar lumen probably by a process of lamellar body exocytosis (44,45). A numbe of studies have shown that a variety of agents ca stimulate surfactant secretion, including adrenergi agonists (46,47), prostaglandins (48), mechanical effects (49), cholinergic agonists (46,50), and other (51,52). The secreted surfactant material takes a variety of different physical forms in the alveolar liqui lining layer including multilamellar vesicles, a latticelike tubular myelin structure, and the monomolecula surface film that is responsible for biophysical activit (53). The interrelationship between the differen physical structures remains unclear.

Clearance of surfactant material from the alveola space of normal lungs appears to occur with a half-lif of ~20 h (54,55). Although precise mechanisms ar unknown, a significant amount of surfactant appear to be cleared and recycled by type II pneumocyte (54–58). Additionally, some clearance and degradation may occur via alveolar macrophages (59). Onl trace amounts of surfactant material seem to b cleared by the airways (60,61). Recent evidence fro our laboratories indicates that surfactant is cleare less rapidly across lungs of rabbits exposed to hyperoxia and that this change in clearance was correlate with the appearance of severe injury to type II pneumocytes (62).

Pulmonary Surfactant System in Lung Disease

Measurement of Surfactant Function

As mentioned above, one of the most importan properties of pulmonary surfactant is its ability t generate very low minimum surface tensions whe the area of the air-liquid interface is reduced unde dynamic compression. The different ways of assessing this property in vitro and the advantages an disadvantages of each method have been summarized by Notter and Finkelstein (25). The two methods used most often are the Langmuir–Wilhelm balance (described in some detail in Figure 1) and th oscillating bubble apparatus of Enhorning (63). Th apparatus allows continuous determination of th pressure drop across the interface of a small ai bubble formed in a surfactant-containing subphase The bubble is pulsed at a given rate (usually 2 cycles/min) between maximum and minimum radii o 0.55 and 0.4 mm. Surface tension is calculated fro the law of Young and Laplace for a sphere: $\Delta P = 2T/r$ where ΔP is the pressure drop across the bubbl interface, T is the surface tension, and r is the bubbl radius. The pulsation is continued until the minimu surface tension reaches a plateau value. The advan tage of this technique over the Wilhelmy balance is the small volume of surfactant material needed for these measurements (around 20 μL).

Physiologic, Biochemical, and Biophysical Changes in Patients with ARDS

The importance of surfactant system alterations in the development of lung disease was first noted in 1959 when Avery and Mead (17) showed that the respiratory distress syndrome (RDS) of the premature newborn, which is characterized by reduced lung compliance, intrapulmonary shunting, atelectasis, and decreased functional residual capacity, was due to a surfactant deficiency in the immature lung. Since that time, great advances have been made in surfactant research, including the development of exogenous surfactant replacement therapy, which has been shown to be highly efficacious in the treatment of neonatal RDS (17–22,64,65).

The many similarities between the pathophysiologic features of the neonatal and adult respiratory distress syndrome led a number of investigators to question whether a dysfunction of the pulmonary surfactant system played a role in the development of ARDS. Ashbaugh et al. (1) were first to report that the minimum surface tension of minced lungs obtained from two patients who died of ARDS was >20 dyne/cm; normal values were <10 dyne/cm. Petty et al. (66) obtained a static pressure-volume curve from the lungs of a patient who died of ARDS and compared it to those of normal lungs. They reported that the ARDS lungs had lower lung volumes and decreased compliance. The bronchoalveolar lavage from the ARDS lungs had normal lipid levels and a higher protein content. In addition, its compressibility in a Wilhelmy balance was much higher than that of the bronchoalveolar lavage of control lungs. A high compressibility value is indicative of instability under stress and seen in films with high protein content. The authors concluded that the high compressibility may have been responsible for the decreased compliance. In addition the authors claimed that the minimum surface tension achieved by the bronchoalveoar lavage from the ARDS lung was in the normal range. However, their reported value of 20 dyne/cm s much higher than the normal values usually reported (<5 dyne/cm).

In a more recent study Hallman et al. (67) meaured phospholipid levels in bronchoalveolar lavage amples obtained from lungs of patients who died of ARDS and compared them to those of normal lungs. There was no significant difference in total phospholipid concentration between ARDS and normal lungs. However, the phospholipid composition of the former was abnormal: the lecithin to sphingomyelin ratio and phosphatidylglycerol and disaturated lecithin values were low compared to normal. Furthermore, lipid-protein complexes, isolated from the bronchoalveolar lavage of ARDS patients were not surface active (i.e., their minimum surface tension was around 20 dyne/cm). Von Wichert and Kohl (68) also found abnormal phospholipid composition in lung tissue samples of ARDS patients. However, in contrast to Hallman et al. (67), they found that ARDS lungs had a higher than normal phospholipid content. Holm et al. (14) also reported higher levels of lavageable phospholipids in the lungs of rabbits that recovered from acute lung injury resembling ARDS. Subsequent studies by Holm et al. (69) have shown increased surfactant production by type II cells isolated from these lungs. The mechanism and importance of increased surfactant production in lungs recovering from injury is not clear.

In spite of the existing quantitative and qualitative differences, the results of all of these studies indicate that the surfactant system of patients with ARDS has been compromised. Although subsequent studies have indicated that surfactant system alterations are not the primary pathogenic factor in ARDS (3), one should not infer that surfactant abnormalities are of only secondary importance. Because the surfactant system is vital to proper lung function, any type of surfactant deficiency, be it primary or secondary, will contribute to the development of pulmonary pathophysiology.

Surfactant Changes in Animals with ARDS-Type Injuries

A number of in vivo models of lung injury have been developed that stimulate most of the pathophysiologic and morphologic features of ARDS. As is the case with human ARDS, these animal models demonstrate a great deal of diversity. For example, the lung injury generated by in vivo lavage (70) or infusion of anti-lung serum (12) occurs almost immediately after the insult, whereas other injuries occur over a matter of hours (bilateral vagotomy [13], oleic acid infusion [71]), or days (paraquat ingestion [72], oxygen toxicity [14,69,73]). However, in each case there has been good documentation of increased alveolar permeability to solute, and the pathophysiologic features of these injuries (atelectasis, decreased compliance, protein-rich pulmonary edema) have been similar.

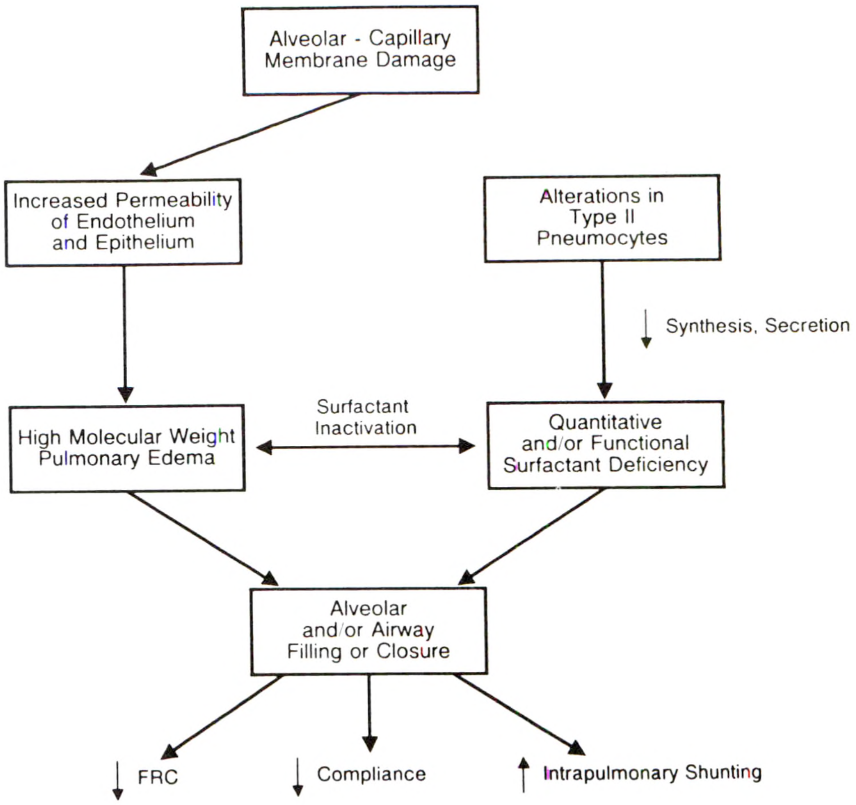
Alveolar - Capillary Membrane Damage
Increased Permeability of Endothelium and Epithelium
Alterations in Type II Pneumocytes
↓ Synthesis, Secretion
High Molecular Weight Pulmonary Edema
Surfactant Inactivation
Quantitative and/or Functional Surfactant Deficiency
Alveolar and/or Airway Filling or Closure
↓ FRC
↓ Compliance
↑ Intrapulmonary Shunting

Figure 2. Proposed pathogenic sequence of events in ARDS. (Modified from Hopewell and Murray, Reference 3, pp. 101–28.)

In addition, all of the lung injury models discussed above showed significant indications of pulmonary surfactant system alteration. In some instances, such as paraquat intoxication (72) and oxygen toxicity (14,69), alveolar surfactant levels are decreased as a result of impaired phospholipid metabolism by type II pneumocytes. In other injuries, such as viral pneumonia (74), quantitative surfactant deficiencies appear to occur secondary to type II cell destruction. Finally, some of the ARDS models, including bilateral vagotomy (13) and oleic acid embolism (71), occur acutely and show no indications of changes in surfactant levels at all. Nevertheless, all of the lung injury models described above demonstrate functional surfactant deficiencies, indicated by increased surface tension values of bronchoalveolar lavage (>20 dyne/cm). These increased surface tension values are caused to a large extent by surfactant inactivation by increased plasma proteins and fluid membrane lipids in the alveolar space as described below.

Mechanisms of Surfactant Deficiency

As noted previously, there are a variety of disorders that can lead to the development of ARDS, with a variety of primary mechanisms of injury involved. Nevertheless, one of the common pathological hallmarks of all ARDS-type lung injuries is the accumulation of protein-rich edema in the alveolar space as a result of increased alveolar permeability (3). Several lines of evidence indicate that many of the constituents of permeability pulmonary edema, such as plasma proteins, cell membrane lipids, and even hemoglobin, are capable of the biophysical inhibition of the surfactant material already present in the alveolus (75–81).

A postulated sequence of events in ARDS-type lung injuries is shown schematically in Figure 2. As indicated in the figure, surfactant inactivation by plasma-derived agents would act to exacerbate the existing lung lesion and generate a vicious circle leading to alveolar closure and the characteristic pathophysiology of ARDS. Moreover, this functional surfactant deficiency could be generated even in the absence of a quantitative surfactant deficiency, and would be capable of causing significant effects in both highly acute and more slowly generated forms of lung injury.

One of the more important findings from biophysical studies of surfactant inactivation is that the plasma protein-induced inhibition of surfactant activity is dependent on the surfactant concentration (75–79,81). As shown in Table 2, the protein-induced inhibition of the surface tension lowering capacity of

Table 2. Effects of Plasma Proteins on Surfactant Activity (Dynamic)

Surfactant mixture	Phospholipid concentration (mg/mL)	Protein concentration (mg/mL)	Minimum surface tension (dyne/cm) at time (min)		
			0	5	10
Albumin	—	2–200	45	45	45
Hemoglobin	—	2–200	37	36	35
Fibrinogen	—	2–200	47	46	46
LS	0.5	—	19	4	0
LS + albumin	0.5	20	45	21	21
LS + hemoglobin	0.5	20	34	29	26
LS + fibrinogen	0.5	20	47	24	24
LS	2.0	—	19	0	0
LS + albumin	2.0	200	45	0	0
LS + hemoglobin	2.0	200	34	0	0
LS + fibrinogen	2.0	200	45	0	0

LS, lung surfactant.

A bubble was formed in an oscillating bubble apparatus at the indicated air-liquid interfaces. The bubble was then pulsated at 20 cycles/min for the indicated time at which point the minimum surface tension was recorded. Data are from Holm et al. (75,76,81). In each case values are means for at least three different trials.

natural surfactant observed at lower phospholipid concentrations is completely abolished when the surfactant concentration is increased. Moreover, this threshold-type resistance to inhibition at higher surfactant concentrations is maintained even when the molar ratio of protein to phospholipid is increased as much as fivefold.

The concept that the inhibition of lung surfactant biophysical activity is dependent on the surfactant concentration presents at least two points of practical relevance. First, it suggests that a quantitative surfactant deficiency will act to exacerbate any functional surfactant deficiency induced by the lung injury. More importantly, it suggests that exogenous surfactant replacement therapy might be efficacious in ameliorating any lung pathophysiology that is related to surfactant system dysfunction.

Indeed both of these points were supported by the results of a number of studies. Seeger et al. (79) induced equal amounts of cardiogenic and permeability-type edema in rabbit lungs. In the latter case the amount of protein in the alveolar space increased 20-fold. The amount of all lavageable phospholipid remained unchanged in both cases. The mechanical properties of isolated lungs (as assessed by measurements of pressure volume curves, total lung capacity, and compliance) were decreased in both groups but more so in the rabbits with permeability-type edema. Also, minimum surface tension of the bronchoalveolar lavage increased in both groups, but more so in the animals with permeability-type edema. These authors concluded that the presence of protein in the alveolar space interferes with surfactant function.

In a different set of experiments, Holm and Notter (76) used an in vitro excised lung preparation to determine the effects of plasma proteins on lung mechanics. The results of these studies, depicted in Figure 3, indicated that intratracheal instillation of plasma proteins caused lung mechanical dysfunction that was made even more severe when the lungs were first made partially surfactant-deficient. Moreover, the mechanical abnormalities present in these lungs were almost abolished after the administration of exogenous surfactant. Thus, there is both in vivo and in vitro biophysical and physiologic evidence to suggest that surfactant replacement therapy might be of benefit in helping to manage ARDS-type lung injury. This concept is discussed further in the sections on in vivo models below.

Surfactant Replacement

Exogenous Surfactant Mixtures

In terms of exogenous surfactant replacement mixtures, there are four basic types of surfactant that are currently being studied for the treatment of neonatal lung disease.

Natural surfactants. These mixtures are recovered from alveolar lavage or amniotic fluid, usually employing a density gradient centrifugation step. These surfactant preparations generally have a higher protein content than other preparations, but contain all surfactant apoproteins.

Modified natural surfactant. These mixtures refer to preparations that are organically extracted from alveolar lavage or lung tissue minces and then reconstituted in normal saline. When the initial collection procedure involves tissue homogenization, selective addition or removal of certain components is often necessary to overcome contamination by cell membrane lipids. The surfactant extract mixtures contain only the low molecular weight, hydrophobic apoproteins.

Artificial surfactants. These are mixtures of synthetic compounds that may or may not be components of natural lung surfactant. These mixtures contain no surfactant apoproteins (82,83).

Recombined/synthetic surfactants. These are mixtures of phospholipid and neutral lipid components of natural surfactant that have been reconstituted with

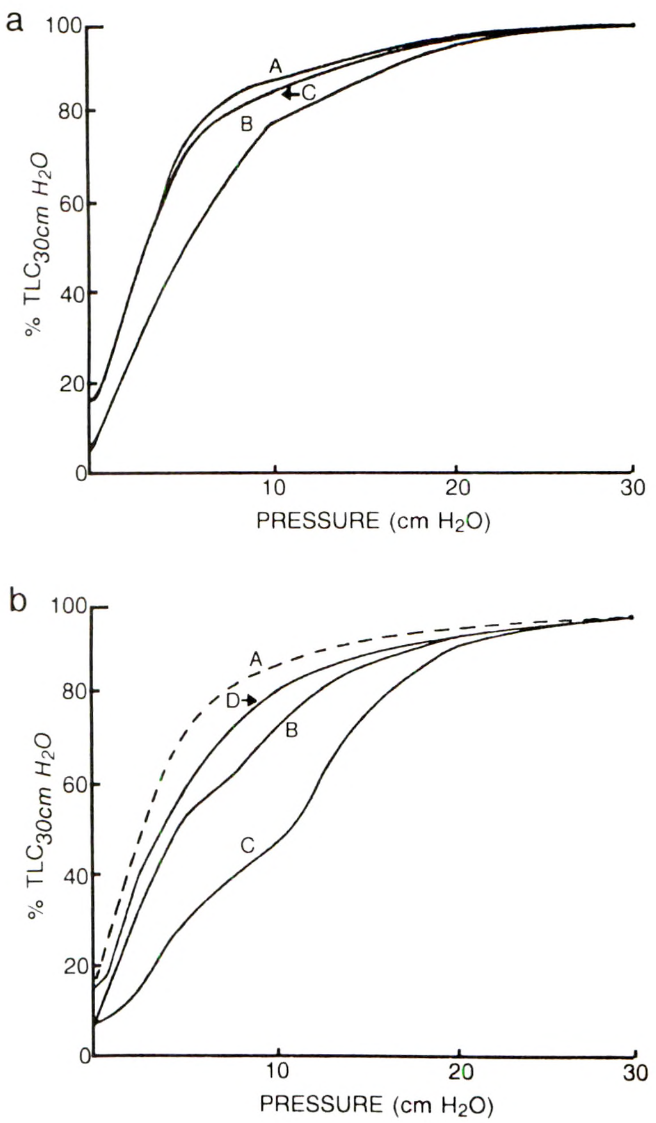

Figure 3. (**a**) Effects of albumin and hemoglobin on pressure-volume deflation curves of excised rat lungs. Isolated rat lungs were instilled with the indicated substances, dissolved in 2 mL of saline, and inflated slowly to 30 cm H_2O transpulmonary pressure. The volume achieved at this pressure was defined at the total lung capacity (TLC$_{30\ \mathrm{cm}}$ H_2O). After a period of stress relaxation, the lungs were deflated to 0 cm H_2O pressure at constant rate. Instillation of proteins decreased lung volumes and lung compliance. These variables were returned to normal after instillation of lung surfactant. Mean values for $n \geq 4$. (**A**) Normal lungs. (**B**) Lungs instilled with 400 mg of albumin or hemoglobin. (**C**) Lungs instilled with 400 mg of albumin or hemoglobin and then supplemented with 25 mg of CLSE. (**b**) Effects of albumin and hemoglobin on pressure volume deflation curves of partially surfactant-deficient rat lungs. (**A**) Normal lungs. (**B**) Partially surfactant-deficient lungs: isolated rat lungs were lavaged once with 15 mL of saline to render them surfactant-deficient. (**C**) Partially surfactant-deficient lung instilled with 400 mg of albumin or hemoglobin. (**D**) Partially surfactant-deficient lung instilled with 400 mg of albumin or hemoglobin and then supplemented with 25 mg of CLSE. Instillation of proteins exacerbated the manifestations of surfactant deficiency. Again, instillation of CLSE restored lung mechanics to almost normal values. Mean values for $n \geq 4$. (Modified from Holm et al., Reference 75 and Holm and Notter, Reference 76.)

one or more surfactant apoproteins. This type of surfactant preparation is relatively new and, unlike the other three types of surfactant mixtures described above, has not been used in clinical trials for the treatment of neonatal RDS.

Although all of the surfactant mixtures described above have certain common features such as the ability to reduce the surface tension of an air-liquid interface to values <5 dyne/cm upon compression, they are fundamentally different with regard to physical properties and, in some cases, physiologic efficacy (83–85). Moreover, recent evidence suggests that some types of surfactant may be more resistant to inhibition phenomena than others, an issue of great importance with regard to the use of surfactant replacement therapy in lung injury situations (86).

Mitigation of ARDS-Type Injury by Surfactant Instillation

As mentioned above, all of the lung injury models described have demonstrated some form of surfactant dysfunction as part of their associated pathophysiology. However, only a few have been used to test the potential efficacy of surfactant therapy in ARDS-type injury.

One of the first studies of surfactant replacement in adult lung injury was done by Lachmann and colleagues (70,87) using an in vivo lung lavage model with adult guinea pigs. After repeated lavage with a volume of normal saline equal to the animal's vital capacity, dynamic lung compliance decreased to ~20% of control values, and the animals became severely hypoxemic. Moreover, the decreased lung mechanical properties and pulmonary function persisted over the 8-h time-course studied, and was not greatly improved even during pressure-controlled mechanical ventilation with pure oxygen (87). However, when the artificial ventilation ($\mathrm{FI}_{\mathrm{O}_2} = 1.0$) was combined with the intratracheal administration of two 50-mg doses of natural surfactant, lung function improved greatly and was maintained over a period of at least 5 h, as shown in Figure 4. In addition, histologic examination of surfactant-treated lungs showed well-aerated alveoli with minimal edema formation.

Arguments have been made that this model of lung injury more accurately reflects the pathological sequelae of neonatal RDS than the pathophysiology of ARDS. Nevertheless, surfactant therapy has also shown positive effects in other lung injury models that do not presuppose a primary surfactant deficiency, such as intravascular injection of anti-lung

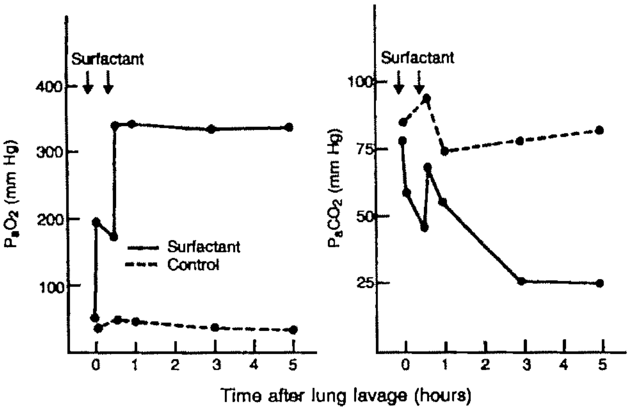

Figure 4. Protective effects of exogenous surfactant in surfactant-deficient lungs. The lungs of two guinea pigs were lavaged extensively and the animals were ventilated for 5 h with 100% O_2. One animal received two intratracheal instillations of natural lung surfactant (50 mg each) at the indicated intervals. Surfactant instillation significantly improved gas exchange as shown by the increase of the Pa_{O_2} and the decrease of the Pa_{CO_2} (From Lachmann and Danzmann, Reference 87, pp. 505–48.)

Table 3. Physiologic, Biochemical, and Biophysical Changes in Rabbits Exposed to 100% O_2 for 64 h and Returned to Room Air for the Indicated Intervals

	Control	64 h 100% O_2	64 h 100% O_2 and 24 h air	64 h 100% O_2 and 200 h air
PL (μmol/kg)	8.7 ± 1.6	6.1 ± 0.05[a]	4.5 ± 0.6[a]	13.6 ± 3.9[a]
PC (μmol/kg)	7.3 ± 0.6	5.4 ± 0.2[a]	3.6 ± 0.2[a]	11.8 ± 1.3[a]
(PC/PL) (%)	84	88	83	87
DPPC (μmol/kg)	5.2 ± 0.3	4.1 ± 0.1[a]	2.8 ± 0.1[a]	8.8 ± 0.6[a]
(DPPC/PC) (%)	71	75	77	75
Pr (mg/kg)	7.4 ± 3.5	27.7 ± 4.7[a]	56.0 ± 3.5[a]	10.5 ± 2.6
Pr/PL (mg/μmol)	0.85	4.5	12.4	0.80
W_L/W_D	4.1 ± 0.3	4.5 ± 0.2	6.3 ± 0.2[a]	4.6 ± 0.2
TLC (mL/kg)	37 ± 2	35 ± 1	23 ± 3[a]	35 ± 2
T_{min} (dyne/cm)	1 ± 0.2	5 ± 2	30 ± 2[a]	1 ± 0.2

PL, total phospholipid in bronchoalveolar lavage; PC, phosphatidylcholine; DPPC, disaturated phosphatidylcholine; Pr, protein; W_L/W_D, lung wet and dry weight; TLC, total lung capacity; T_{min}, minimum surface tension. (Modified from Holm et al., Reference 14.)

Values are mean ± 1 SEM; $n > 5$.

[a] Significantly different from control ($P < 0.05$).

serum (12) or *N*-nitroso-*N*-methylurethane (88). In addition, Berry et al. (13) demonstrated the efficacy of surfactant replacement in treating the respiratory distress associated with bilateral cervical vagotomy. Within 4 h after the vagotomy, adult rabbits developed decreased lung compliance and severe hypoxemia that was relatively refractory to ventilation with 100% oxygen (O_2). In addition, histologic analyses demonstrated alveolar edema, hemorrhage, and hyaline membrane formation. As mentioned above, the lung damage in this model was associated with a functional surfactant deficit, but occurred in the absence of a quantitative decrease in alveolar surfactant levels. Nevertheless, surfactant treatment in these animals resulted in significant improvements in lung compliance and pulmonary function.

In a recent series of studies, Matalon, Holm, and co-workers evaluated the efficacy of exogenous surfactant supplementation in limiting alveolar epithelial injury and improving survival in rabbits exposed to 100% O_2. The pathophysiologic manifestations of pulmonary oxygen toxicity closely resemble those seen in clinical ARDS with the exception that most animals do not develop pulmonary hypertension during acute exposures (73,89–95). These experiments are described in detail below.

Rabbits exposed to 100% O_2 at 1 ATA maintain normal arterial blood gases and vascular pressures till shortly before death when the Pa_{O_2} drops and the rabbits die of acute respiratory failure. Studies by Matalon and Egan (89,90) and Matalon and Cesar (91) indicate that exposure to 100% O_2 results in progressive increase in both the alveolar permeability to solute and the capillary permeability to solvent. These changes first occurred between 24 and 48 h of O_2 exposure and preceded the appearance of significant alterations in structure and the development of respiratory failure. Currently, it is accepted that hyperoxic injury, like many cases of clinical ARDS, is the result of increased intracellular and extracellular production of partially reduced O_2 species (96).

Holm et al. (14) exposed rabbits to 100% O_2 for 64 h and then removed them to room air for varying periods of time up to 200 h. The alveolar permeability to solute increased significantly by the end of the 64-h exposure period, and biochemical analyses of bronchoalveolar lavages showed a significant decline in phospholipid content and an increase in protein level (Table 3). However, other variables such as wet/dry weight ratios, arterial blood gases, and lung volumes were at their normal levels. At 24 h after exposure, while the rabbits were breathing room air, alveolar phospholipid levels declined further and protein levels in lavages increased dramatically. These lavages exhibited severely impaired dynamic surface activity at 37°C and 100% humidity in an oscillating bubble apparatus. In addition, all rabbits developed arterial hypoxemia and 35% of them died within the first hour postexposure. In the rabbits that survived, all measured physiologic variables returned to normal by 200 h after exposure, except for the phospholipid values that were considerably higher than normal. Measurements of precursor incorporation into freshly isolated type II cells revealed a 60% decrease in phosphatidylcholine synthesis after 64 h in O_2 followed by recovery after 3 days to normal and eventually above-normal levels (75). These findings suggest that O_2-induced changes in type II cell surfactant biosynthesis may account, at least in part, for observed changes in lung phospholipid levels in vivo. However, like the other ARDS models discussed, surfactant inactivation by high levels of plasma proteins in the alveolar space also played a role (75).

Using this model, Matalon et al. (15) reported significant amelioration of lung injury by instillation of exogenous surfactant. At the end of a 64-h exposure to 100% O_2, the rabbits were anesthetized and 125 mg of calf lung surfactant extract (CLSE), dissolved in 6–8 mL of 0.15 M sterile NaCl (~170 μmol of lipid) was instilled in the lungs through the trachea. The CLSE was obtained by chloroform-methanol extraction of cell-free bronchoalveolar lavage of lungs of freshly killed calves (18). It consists of 99% lipid and 1% protein including the low molecular weight hydrophobic apoproteins (SP-B, SP-C). This extract has been shown to improve lung mechanics significantly both in premature lambs and infants with RDS (18,19). The rabbits were rotated slowly during the instillation procedure through a 360° arc to enhance the distribution of instillate among the different lung fields. A second instillation was given 12 h after exposure to maintain high lipid levels in the alveolar space. Control rabbits received an equal volume of saline under similar conditions.

The distribution of lung surfactant among the different lung fields was assessed by adding a small amount of Evans blue in the instillate and inspecting the different lung lobes for the presence of dye. There was intense staining of the dorsal and medial sections of the upper, middle, and lower lobes in both lungs. Transverse sections of the lower lobes showed staining around the main bronchi, with its intensity diminishing toward the periphery.

The results of this study are shown in Table 4 and Figure 5. Surfactant instillation prevented the development of abnormal lung mechanics and alveolar collapse and significantly decreased the amount of protein in the bronchoalveolar lavage. Moreover, the mortality from respiratory failure decreased from 45% to 10%.

Table 4. Effects of Surfactant Treatment on Hyperoxic Lung Injury

		64 h in 100% O_2 + 24 h in air		
	Control (unexposed)	Untreated	Saline-treated	Surfactant-treated
Alveolar phospholipid (mg/kg)	6.5 ± 1.2	3.4 ± 0.5[a]	4.5 ± 0.8[a]	26 ± 3.0[b]
Alveolar protein (mg/kg)	7.4 ± 3.5	56 ± 3.5[a]	60 ± 2.0[a]	35 ± 3.0[a]
Minimum surface tension (mN/m)	1.0 ± 0.2	30 ± 2.0[a]	26 ± 2.0[a]	1.0 ± 0.2[b]
Lung wet/dry weight	4.1 ± 0.3	6.2 ± 0.2[a]	6.6 ± 0.3[a]	5.6 ± 0.1[a]
Total lung capacity (mL)	80 ± 4.0	48 ± 6.0[a]	57 ± 2.0[a]	88 ± 4.0[a]
Pa_{O_2} (torr)				
$FI_{O_2} = 0.21$	80 ± 3.0	56 ± 9.0[a]	52 ± 6.0[a]	54 ± 3.0[a]
$FI_{O_2} = 1.0$	474 ± 16	200 ± 40[a]	197 ± 55[a]	446 ± 31[b]

Values are mean ± SE; $n \geq 4$. Rabbits were exposed to 100% O_2 for 64 h and then returned to room air. Two boluses of calf lung surfactant extract (125 mg each) suspended in saline were instilled intratracheally immediately upon return to room air and 12 h later. Untreated rabbits received no instillations.

[a] Significantly different from control, $P < 0.05$.

[b] Significantly different from saline-treated animals, $P < 0.05$.

It is interesting to note that both surfactant- and saline-treated rabbits were hypoxemic while breathing room air (Pa_{O_2} ~55 torr; see Table 4). However, after breathing 100% O_2 for 30 min, the mean Pa_{O_2} of the surfactant group was >400 torr while the corresponding value in the saline group was only 200 torr. These data indicate that the hypoxemia in the surfactant group was caused by areas of low ventilation/perfusion ratio, whereas in the saline group the cause was a right-to-left shunt. As expected, surfactant instillation alleviated the surfactant-deficient state and prevented alveoli from collapsing.

In the above-mentioned study, surfactant was instilled after a significant degree of lung injury had developed. Loewen et al. (16) investigated whether prophylactic administration of exogenous lung surfactant could prevent or at least minimize the onset of hyperoxic lung injury. These authors exposed rabbits to 100% O_2 and instilled intratracheally multiple doses of 125 mg of CLSE, dissolved in 10 mL of sterile saline, as described by Matalon et al. (15). The first instillation was performed after 24 h in 100% O_2, a time at which no physiologic or biochemical injury could be detected (93); subsequent instillations were performed every 24 h thereafter. The rabbits receiving CLSE survived considerably longer in 100% O_2 when compared with saline controls. In addition, after 72 h in O_2, the rabbits receiving CLSE had lower levels of alveolar protein and lung wet/dry weight ratios and higher total lung capacities compared with either those receiving saline or those receiving no instillation. In a more recent study, Baker et al. (97) reported that rabbits with higher levels of endogenous surfactant, but normal levels of lung antioxidant enzymes,

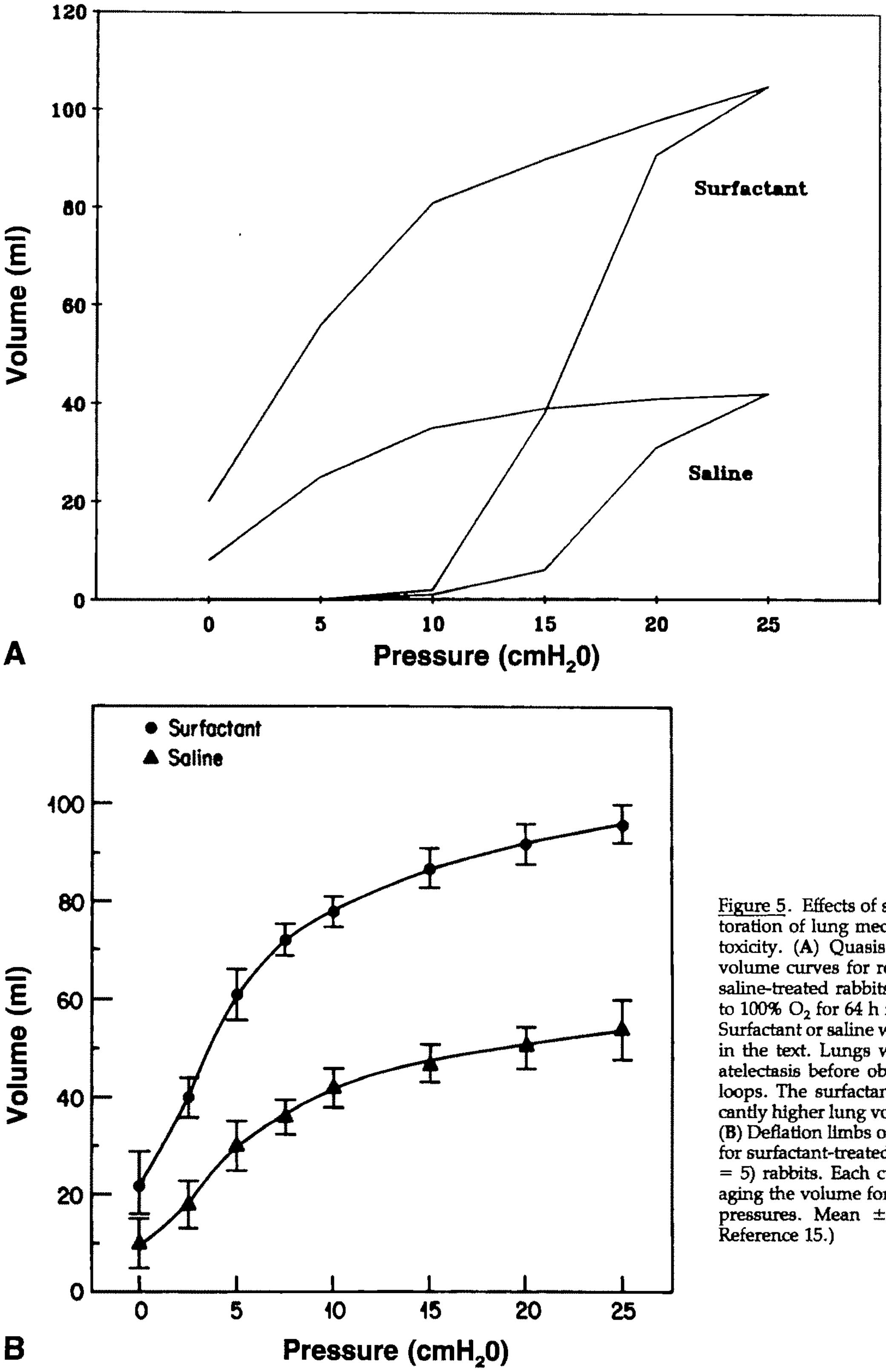

Figure 5. Effects of surfactant replacement in restoration of lung mechanics in pulmonary oxygen toxicity. (A) Quasistatic, open-chested pressure volume curves for representative surfactant- and saline-treated rabbits. Both rabbits were exposed to 100% O_2 for 64 h followed by 24 h in room air. Surfactant or saline was administered as described in the text. Lungs were collapsed by absorption atelectasis before obtaining the pressure volume loops. The surfactant-treated rabbits had significantly higher lung volumes in this pressure range. (B) Deflation limbs of quasistatic pressure-volume for surfactant-treated ($n = 7$) and saline-treated ($n = 5$) rabbits. Each curve was calculated by averaging the volume for each animal at the indicated pressures. Mean ± SE. (From Matalon et al., Reference 15.)

survived considerably longer in hyperoxia than normal rabbits. It should be emphasized, however, that, like ARDS, the pathophysiology of hyperoxic lung injury is multifocal and involves damage to all components of the blood-gas barrier. Instillation of surfactant only delays the onset of respiratory failure.

Surfactant Treatment in Clinical Adult Respiratory Distress Syndrome

Presently, there are only preliminary reports about the efficacy of exogenous surfactant instillation in the management of patients with ARDS. Richman et al. (23) found a transient increase in Pa_{O_2} in two patients with ARDS after administration of a single dose of 4 g of exogenous surfactant. These authors suggested that multiple instillations are needed for a sustained beneficial effect. Lachmann (98) reported that tracheal instillation of natural surfactant (300 mg/kg body wt of phospholipid) in a patient with sepsis and severe ARDS led to a significant improvement of gas exchange. In both of these cases the surfactant was dissolved in sterile saline. These two isolated reports indicate that instillation of exogenous surfactant in patients with ARDS is feasible and has a temporary beneficial effect. Clearly, additional studies are needed to document whether surfactant instillation improves the morbidity and mortality of patients with ARDS.

Exogenous surfactant supplementation may limit the degree of lung injury by a number of different mechanisms. First of all, as previously mentioned, it restores lung mechanics by replacing depleted alveolar lipid stores and thus overcomes the surfactant inactivation by plasma proteins that have entered the alveolar space. Surfactant deficiency is known to result in alveolar collapse, hypoxemia, and promotion of the formation of pulmonary edema (99). Recent studies by Matalon et al. (100) have also identified the existence of a large amount of superoxide dismutase and catalase-type activity in natural lung surfactant but not in surfactant extracts such as CLSE. As surfactant is taken up by type II pneumocytes, instillation of natural surfactant may reduce the steady-state intracellular and extracellular concentrations of reactive oxygen species, which are thought to be one of the most important factors in the pathogenesis of some forms of ARDS.

Summary

The goal of this article has been to examine the role of pulmonary surfactant system alterations in the development of ARDS, and the potential efficacy of surfactant replacement therapy in ARDS and ARDS-type injuries. Data from patients with ARDS and animal models with ARDS-type injuries clearly indicate the existence of a surfactant-deficient state. However, in contrast to neonatal RDS, this deficiency generally does not represent the primary pathogenic factor.

The diversity of the disorders associated with ARDS has made it impossible to develop a single-animal model that can be used to test potential therapeutic measures. The ARDS animal models that have been developed are equally diverse, and represent the wide variations in severity and time-course seen clinically. Nevertheless, almost all of the lung injury models show indications of surfactant abnormality, which is caused mainly by biophysical inhibition of surfactant activity by the large amounts of proteinaceous edema found in the injured lungs. In some cases, this surfactant dysfunction is further compounded by a quantitative surfactant deficiency brought about by metabolic alterations of the type II pneumocytes.

It is important to note that all of the lung injury models studied thus far have shown significant improvements in pulmonary mechanics and arterial oxygenation after treatment with exogenous surfactant. Such results are consistent with biophysical studies that suggest that increasing the effective surfactant concentration in the lung should mitigate the effects of both quantitative and functional surfactant deficiencies.

Although animal studies suggest that surfactant replacement therapy might be efficacious in ARDS, there is a good deal of experimental work that still needs to be done. Most of what we know about clinical surfactant therapy has been developed through the treatment of neonatal RDS, and the practical problems of scaling up surfactant delivery for adult applications are significant. It is clear that sustained beneficial effects necessitate multiple instillations of large amounts of exogenous surfactant (between 50 and 300 mg/kg body wt of lipid). There is concern that the distribution of the instilled surfactant will be grossly nonuniform, with injured areas receiving little or no surfactant. Thus, the optimization of the delivery method, dosage, and timing of delivery should first be further considered in the laboratory before considerations of clinical trials. Nevertheless, data presently available from animal studies and a limited number of patients show that in spite of these problems surfactant administration may improve the outcome of patients with ARDS.

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References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967;ii:319–23.

2. Royall JA, Levin DL. Adult respiratory distress syndrome in pediatric patients. I. Clinical aspects, pathophysiology, pathology, and mechanics of lung injury. J Pediatr 1988; 112:169–80.
3. Hopewell PC, Murray J. The adult respiratory distress syndrome. In: Shibel EM, Moser KM, eds. Respiratory emergencies. St. Louis, Mo.: CV Mosby, 1977:101.
4. Bradley RB. Adult respiratory distress syndrome. Focus Crit Care 1987;14:48–9.
5. Shale DJ. The adult respiratory distress syndrome—20 years on. Thorax 1987;42:642–5.
6. Rinaldo JE, Rogers RM. Adult respiratory distress syndrome: changing concepts of lung injury and repair. N Engl J Med 1982;306:900–9.
7. Pfenninger J, Gerber A, Tschappeler H, Zimmerman A. Adult respiratory distress syndrome in children. J Pediatr 1982; 101:352–7.
8. Lyrene RK, Troug WE. Adult respiratory distress syndrome in a pediatric intensive care unit: predisposing conditions, clinical course, and outcome. Pediatrics 1981;67:790–5.
9. Nussbaum E. Adult-type respiratory distress syndrome in children. Clin Pediatr 1983;22:401–6.
10. Deneke SM, Fanburg BL. Normobaric oxygen toxicity of the lung. N Engl J Med 1980;303:76–80.
11. Lachmann B, Fujuwara T, Chida S. Surfactant replacement therapy in experimental adult respiratory distress syndrome (ARDS). In: Cosmi EV, Scarpelli EM, eds. Pulmonary surfactant system. Amsterdam: Elsevier, 1983:221.
12. Lachmann B, Hallman M, Bergmann KC. Respiratory failure following anti-lung serum: study on mechanisms associated with surfactant system damage. Exp Lung Res 1987; 12:163–80.
13. Berry D, Ikegami M, Jobe A. Respiratory distress and surfactant inhibition following vagotomy in rabbits. J Appl Physiol 1986;61:1741–8.
14. Holm BA, Notter RH, Seigle J, Matalon S. Pulmonary physiological and surfactant changes during injury and recovery from hyperoxia. J Appl Physiol 1985;59:1402–9.
15. Matalon S, Holm BA, Notter RH. Mitigation of pulmonary hyperoxic injury by administration of exogenous surfactant. J Appl Physiol 1987;62:756–61.
16. Loewen GM, Holm BA, Milanowski I, Wild LM, Matalon S. Alveolar hyperoxic injury in rabbit receiving exogenous surfactant. J Appl Physiol 1988;66:1087–92.
17. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. Am J Dis Child 1959;97: 517–23.
18. Kwong MS, Egan EA, Notter RH. A double blind clinical trial of calf lung lipid for the prevention of hyaline membrane disease in extremely premature infants. Pediatrics 1985; 76:585–92.
19. Shapiro DL, Notter RH, Morin F. A double blind randomized trial of calf lung surfactant extract administered at birth to very premature infants for prevention of respiratory distress syndrome. Pediatrics 1985;76:593.
20. Enhorning GE, Shennan A, Possmayer F. Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant: a randomized clinical trial. Pediatrics 1985; 76:145–53.
21. Merrit TA, Hallman M, Bloom BT. Prophylactic treatment of very premature infants with human surfactant. N Engl J Med 1986;315:785–90.
22. Jobe A, Ikegami M. State of the art. Surfactant for the treatment of respiratory distress syndrome. Am Rev Respir Dis 1987;136:1256–75.
23. Richman PS, Spragg RG, Merritt TA, Robertson B, Curstedt T. Administration of porcine-lung surfactant to humans with ARDS: initial experience (abstract). Am Rev Respir Dis 1987; S135:A5.
24. Lachman B. The role of pulmonary surfactant in the pathogenesis and therapy of ARDS. In: Vincent JL, ed. Update in intensive care and emergency medicine. Berlin: Springer-Verlag, 1987:123.
25. Notter RH, Finkelstein JN. Pulmonary surfactant: an interdisciplinary approach. J Appl Physiol 1984;57:1613–24.
26. King RJ, Clements JA. Surface active materials from dog lung. 1. Method of isolation. Am J Physiol 1972;223:707–14.
27. King RJ. Isolation and chemical composition of pulmonary surfactant. In: Robertson B, Van Golde LMG, Batenburg JJ, eds. Pulmonary surfactant. Amsterdam: Elsevier, 1984:1.
28. Wright JR, Clements JA. Metabolism and turnover of lung surfactant. Am Rev Respir Dis 1987;135:426–4.
29. Possmayer F. Pulmonary perspective: a proposed nomenclature for pulmonary surfactant-associated proteins. Am Rev Respir Dis 1988;138:990–8.
30. Whitsett JA, Hull W, Ross G, Weaver T. Characteristics of human surfactant-associated glycoproteins. Pediatr Res 1985; 19:501–8.
31. Weaver TE, Whitsett JA, Hull WM, Ross G. Identification of canine pulmonary surfactant associated glycoprotein A precursors. J Appl Physiol 1985;58:2091–5.
32. Floros J, Phelps DS, Kourembanas S, Taeusch HW. Primary translation products, biosynthesis, and tissue specificity of the major surfactant protein in rat. J Biol Chem 1986; 261:828–31.
33. Hagwood S, Efrati H, Schilling J, Benson BJ. Chemical characterization of lung surfactant apoproteins: amino acid composition, N-terminal sequence and enzymic digestion. Trans Biochem Soc 1985;13:1092–6.
34. Dobbs LG, Wright JR, Hagwood S, Gonzalez R, Venstrom K, Nellenbogen J. Pulmonary surfactant and its components inhibit secretion of phosphatidylcholine form cultured rat alveolar type II cells. Proc Natl Acad Sci USA 1987;84:1010–4.
35. Wright JR, Wager RE, Hagwood S, Dobbs L, Clements JA. Surfactant apoprotein $M_r = 26,000–36,000$ enhances uptake of liposomes by type II cells. J Biol Chem 1987;262:2888–94.
36. Hagwood S, Benson BJ, Hamilton RL. Effects of a surfactant-associated protein and calcium ions on the structure and surface activity of lung surfactant lipids. Biochemistry 1985; 24:184–90.
37. Whitsett JA, Ohning BL, Ross G, et al. Hydrophobic surfactant-associated protein in whole lung surfactant and its importance for biophysical activity in lung surfactant extracts used for replacement therapy. Pediatr Res 1986;20:460–7.
38. Crecelius CA, Longmore WM. Phosphatidic acid phosphatase activity in subcellular fractions derived from adult rat type II pneumocytes in primary culture. Biochim Biophys Acta 1983;750:447–56.
39 Chevalier G, Collet AJ. In vivo incorporation of choline-^{3}H and galactose-^{3}H in alveolar type II pneumocytes in relation to surfactant synthesis. A quantitative radioautographic study in mouse by electron microscopy. Anat Rec 1972;174:289–310.
40. Massaro GD, Massaro D. Granular pneumocytes. Electron microscopic radioautographic evidence of intracellular protein transport. Am Rev Respir Dis 1972;105:927–31.
41. Whitsett JA, Ross G, Weaver T, Rice W, Dion D, Hull W. Glycosylation and secretion of surfactant-associated glycoprotein A. J Biol Chem 1985;260:15273–9.
42. Weaver TE, Hull WM, Ross G, Whitsett JA. In vitro acetylation of rat pulmonary surfactant-associated glycoprotein(s) A primary translation products. Biochim Biophys Acta 1986; 869:330–6.
43. Walker SR, Williams MC, Benson B. Immunocytochemical localization of the major surfactant apoproteins in type II

cells, Clara cells, and alveolar macrophages of rat lung. J Histochem Cytochem 1986;34:1137–40.

44. Williams MC, Benson BJ. Immunocytochemical localization and identification of the major surfactant protein in adult rat lung. J Histochem Cytochem 1981;29:291–305.
45. Ryan US, Ryan JW, Smith DS. Alveolar type II cells: studies on the mode of release of lamellar bodies. Tissue Cell 1975; 7:587–99.
46. Brown LAS, Longmore WJ. Adrenergic and cholinergic regulation of lung surfactant secretion in the isolated perfused rat lung and in the aveolar type II cell in culture. J Biol Chem 1981;256:66–72.
47. Padbury JF, Jacobs HC, Lam RW, Conaway D, Jobe AH, Fisher DA. Adrenal epinephrine and the regulation of pulmonary surfactant release in neonatal rabbits. Exp Lung Res 1984;7:177–86.
48. Oyarzun MJ, Clements JA. Control of lung surfactant by ventilation, adrenergic mediators and prostaglandins in the rabbit. Am Rev Respir Dis 1978;17:879–91.
49. Nicholas TE, Power JHT, Barr HA. Surfactant homeostasis in the rat lung during swimming exercise. J Appl Physiol 1982; 53:1521–8.
50. Oyarzun MJ, Clements JA. Ventilatory and cholinergic control of pulmonary surfactant in the rabbit. J Appl Physiol 1977;43:39–45.
51. Mason RJ, Williams MC, Greenleaf RD, Clements JA. Isolation and properties of type II alveolar cells from rat lung. Am Rev Respir Dis 1977;115:1015–26.
52. Dobbs LG, Mason RJ. Stimulation of secretion of desaturated phosphatidylcholine form isolated type II cells by 12-0-tetradecanoyl-13-phorbol acetate. Am Rev Respir Dis 1978; 118:705–13.
53. Magoon MW, Wright JR, Baritussio A. Subfractionation of lung surfactant. Implications for metabolism and surface activity. Biochim Biophys Acta 1983;750:18–31.
54. Baritussio AG, Magoon MW, Goerke J, Clements JA. Precursor-product relationship between rabbit type II cell lamellar bodies and alveolar surface active material. Surfactant turnover time. Biochim Biophys Acta 1981;666:382–93.
55. Jobe A, Kirkpatrick E, Gluck L. Labeling of phospholipids in the surfactant and subcellular fractions of rabbit lung. J Biol Chem 1978;253:3810–6.
56. Hallman M, Epstein BL, Gluck L. Analysis of labeling and clearance of lung surfactant phospholipids in rabbit. Evidence of bi-directional surfactant flux between lamellar bodies and alveolar lavage. J Clin Invest 1981;68:742–51.
57. Young SL, Kremers SA, Apple JS, Crap JD, Brumley GW. Rat lung surfactant kinetics: biochemical and morphometric correlation. J Appl Physiol 1981;51:248–53.
58. Jacobs H, Jobe A, Ikegami M, Jones S. Surfactant phosphatidylcholine source, fluxes, turnover times in 3-day-old, 10-day-old, and adult rabbits. J Biol Chem 1982;257:1805–10.
59. Miles PR, Bowman L, Castranova V. Incorporation of [^{3}H]palmitate and [^{14}C]choline into disaturated phosphatidylcholines in rat alveolar macrophages. Biochim Biophys Acta 1985;833:342–50.
60. Fisher HK, Hyman MH, Ashcraft SJ. Alveolar surfactant phospholipids are not cleared via trachea (abstract). Fed Proc 1979;38:1373a.
61. Pettenazze A, Jobe A, Humme J, Seidner S, Ikegami M. Clearance of surfactant phosphatidylcholine via the upper airways in rabbits. J Appl Physiol 1988;65:2151–5.
62. Holm BA, Tonucci D, Matalon S. Clearance of exogenous surfactant in hyperoxic lung injury (abstract). FASEB J 1989; 3:A546.
63. Enhorning G. Pulsating bubble technique for evaluating pulmonary surfactant. J Appl Physiol 1977;43:198–203.
64. Ikegami M, Adams FH, Towers B. The quantity of natural surfactant necessary to prevent the respiratory distress syndrome in premature lambs. Pediatric Res 1980;14:1082–5.
65. Notter RH, Egan EA, Kwong MS. Lung surfactant replacement in premature lambs with extracted lipids from bovine lung lavage: effects of dose, dispersion technique, and gestational age. Pediatr Res 1985;19:569–77.
66. Petty TL, Reiss OK, Paul GW, Silvers GW, Elkins ND. Characteristics of pulmonary surfactant in adult respiratory distress syndrome associated with trauma and shock. Am Rev Respir Dis 1977;115:531–6.
67. Hallman M, Spragg R, Harrell JH, Moser KM, Gluck L. Evidence of lung surfactant abnormality in respiratory failure. J Clin Invest 1982;70:673–83.
68. Von Wichert P, Kohl FV. Decreased dipalmitoyllecithin content found in lung specimens from patients with so-called shock-lung. Eur Intensive Care Med 1977;3:27–30.
69. Holm BA, Matalon S, Finkelstein JN, Notter RH. Type II pneumocyte changes during hyperoxic lung injury and recovery. J Appl Physiol 1988;65:2672–8.
70. Lachmann B, Robertson B, Vogel J. In vivo lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesthesiol Scand 1980;24:231–6.
71. Uzawa T, Ashbaugh DG. Continuous positive-pressure breathing in acute hemmorhage pulmonary edema. J Appl Physiol 1969;26:427–32.
72. Robertson B. Paraquat poisoning as an experimental model of the idiopathic respiratory distress syndrome. Bull Physiopathol Respir 1973;1433.
73. Clark JM, Lambersten CI. Pulmonary oxygen toxicity: a review. Pharmacol Rev 1971;23:37–133.
74. Stinson SF, Ryan DP, Hertweck MS, Hardy JD, Hwang-Kow SY, Loosli CG. Epithelial and surfactant changes in influenza pulmonary lesions. Arch Pathol Lab Med 1976;100:147–53.
75. Holm BA, Notter RH, Finkelstein JN. Surface property changes from interactions of albumin with natural lung surfactant and extracted lung lipids. Chem Phys Lipids 1985; 38:287–98.
76. Holm BA, Notter RH. Effects of hemoglobin and cell membrane lipids on pulmonary surfactant activity. J Appl Physiol 1987;63:1434–42.
77. Ikegami M, Jobe A, Jacobs H. A protein from airways of premature lambs that inhibits surfactant function. J Appl Physiol 1984;57:1134–42.
78. Fuchimukai T, Fujiwara T, Takahashi A, Enhorning G. Artificial pulmonary surfactant inhibited by proteins. J Appl Physiol 1987;62:429–37.
79. Seeger W, Stohr G, Wolf HRD. Alteration of surfactant function due to protein leakage: special interaction with fibrin monomer. J Appl Physiol 1985;58:326–38.
80. Clements JA, Tierney DF. Alveolar instability associated with altered surface tension. In: Fenn WO, Rahn H, eds. Handbook of physiology. Volume 2. Section 3. Respiration. Bethesda, Md.: American Physiological Society, 1965:1567.
81. Holm BA, Enhorning GE, Notter RH. A biophysical mechanism by which plasma proteins inhibit surfactant activity. Chem Phys Lipids 1988;49:49–55.
82. Wilkinson A, Jenkins PA, Jeffrey JA. Two controlled trials of dry artificial surfactant: early effects and later outcome in babies with surfactant deficiency. Lancet 1985;ii:287.
83. Durand DJ, Clyman RI, Heymann MA, et al. Effects of a protein free synthetic surfactant on survival and pulmonary function in preterm lambs. J Pediatr 1985;10:776–80.
84. Ikegami M, Agata Y, Elkady T, Hallman M, Berry D, Jobe A. Comparison of four surfactants: in vitro surface properties and responses of preterm lambs to treatment at birth. Pediatrics 1987;79:38–46.

85. Bloom BT. Human surfactant and calf lung surfactant extract: moderation of respiratory distress in preterm infants by a single prophylactic dose in a randomized and controlled clinical trial. In: Lachmann B, ed. Surfactant replacement therapy in neonatal and adult respiratory distress syndrome. Berlin: Springer-Verlag, 1988:150.

86. Holm BA, Notter RH, Enhorning G. Biophysical and physiological properties of synthetic surfactant. Prog Respir Res 1989 (in press).

87. Lachmann B, Danzmann E. Adult respiratory distress syndrome. In: Robertson B, van Golde LMG, Batenburg JJ, eds. Pulmonary surfactant. Amsterdam: Elsevier, 1984:505.

88. Ryan SF, Liau DF, Bell AL, Hashim SA, Barret CR. Correlation of lung compliance and quantities of surfactant phospholipids after acute alveolar injury from *N*-nitroso-*N*-methylurethane in the dog. Am Rev Respir Dis 1981;123:200–4.

89. Matalon S, Egan EA. Effects of 100% breathing on permeability of alveolar epithelium to solute. J Appl Physiol 1981; 50:859–63.

90. Matalon S, Egan EA. Interstitial fluid volumes and albumin spaces in pulmonary oxygen toxicity. J Appl Physiol 1984; 57:1767–72.

91. Matalon S, Cesar MC. Effects of 100% oxygen breathing on the capillary filtration coefficient in rabbit lungs. Microvasc Res 1985;29:70–80.

92. Matalon S, Nesarajah MS, Farhi LE. Pulmonary and circulatory changes in conscious sheep exposed to 100% O_2 at 1 ATA. J Appl Physiol 1982;53:110–6.

93. Matalon S, Nickerson PA. Alterations in mammalian blood-gas barrier exposed to hyperoxia. In: Taylor AF, Matalon S, Ward P, eds. Physiology of oxygen radicals. Bethesda, Md.: American Physiological Society, 1986:55–86.

94. Bressack MA, McMillan DD, Bland RD. Pulmonary oxygen toxicity: increased microvascular permeability to proteins in unanesthetized lambs. Lymphology 1979;12:133–9.

95. Erdman J III, Huttemeir PC, Landolt C, Zapol WM. Pure oxygen breathing increases sheep lung microvascular permeability. Anesthesiology 1983;58:153–8.

96. Freeman BA, Crapo JD. Biology of disease: free radicals and tissue injury. Lab Invest 1982;47:412–26.

97. Baker RR, Holm BA, Panus PC, Matalon S. Development of O_2 tolerance in rabbits without an increase in antioxidant enzymes. J Appl Physiol 1989;66:1679–84.

98. Lachmann B. The role of pulmonary surfactant in the pathogenesis and therapy of ARDS. In: Vincent JL, ed. Update in intensive care and emergency medicine. Berlin: Springer-Verlag, 1987:123.

99. Nieman GF, Bredenberg CE. High surface tension pulmonary edema induced by detergent aerosol. J Appl Physiol 1985; 58:129–36.

100. Matalon S, Holm BA, Baker RR, Freeman BA. Antioxidant properties of surfactant replacement mixtures. Am Rev Respir Dis 1988;137:80.

Clinical Reports

Effect of Epinephrine on the Duration of Dibucaine (Cinchocaine) Spinal Anesthesia

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Key Words: ANESTHETIC TECHNIQUES, SPINAL—dibucaine. ANESTHETICS, LOCAL—dibucaine.

Epinephrine added to local anesthetic solutions may prolong the duration of spinal anesthesia. The efficacyof this practice appears to vary with the local anesthetic chosen. Published reports conflict as to whether epinephrine increases the duration of anesthesia or has no significant effect when added to either bupivacaine (1,2) or lidocaine (3,4). Tetracaine does seem to have a prolonged action when vasoconstrictors are added (5). Hyperbaric dibucaine (cinchocaine) (Nupercaine) 5% in dextrose has a longer duration than that of hyperbaric bupivacaine (6), and its duration is reputed, although not documented, to be prolonged by the addition of 100–200 μg of epinephrine (7,8). The present randomized, double-blind controlled study was designed to determine whether the duration of hyperbaric dibucaine spinal anesthesia was prolonged by the additional 200 μg epinephrine.

Methods

Thirty-five patients presenting for major lower limb surgery were studied. The study was approved by the Royal Melbourne Hospital Board of Medical Research and the Ethics Committee on Medical Research. After giving written informed consent, patients entering the study were randomized into one of two groups by shuffled card selection. Group 1 patients were given 1.6 mL of hyperbaric dibucaine 5% in dextrose (Astra) to which 0.2 mL normal saline solution was added. Patients in group 2 were given 1.6 mL of hyperbaric dibucaine to which was added 0.2 mL of 1/1000 epinephrine (0.2 mg) (David Bull, Melbourne). Lumbar puncture was performed with a 22-gauge needle in the lateral position with the operative side down. All blocks were performed by the author or under his direct supervision. The intervertebral space chosen was L2–3 or L3–4, depending on which was considered to be the easiest space to perform the block. Once the subarachnoid space was entered and a free flow of cerebrospinal fluid (CSF) obtained, 1.8 mL of solution was injected over 20 s with aspiration at the start of injection, after injection of 0.9 mL, and on completion of injection. The patient was then turned to the supine position, and the level of sensory loss was determined on the operative side by light pin prick 5, 10, 15, 20, and 30 min after completion of injection. The level of anesthesia was then assessed at 15 min intervals thereafter until it receded below the level of T-12 or until 4 h had passed since the lumbar puncture. If anesthesia was still present above the first lumbar dermatome at 4 h, the block was coded as having regressed to the L-1 dermatome at 255 min. Blood pressure and pulse were recorded at 5 min intervals by a Nippon Collins oscillotonometer.

Before induction of anesthesia, 7 mL/kg normal body weight of lactated Ringer's solution was given IV; thereafter, fluids and pressors were administered by an investigator who was unaware of the nature of the agent administered to the patient.

Patients were excluded from analysis if anesthesia was not successful, i.e., did not extend above T-12 or the patient required additional (inhalation) anesthesia.

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Table 1. Patient's Median (95% Confidence Limits) Age, Height, and Body Weight

Group	*n*	Age (yr)	Height (cm)	Weight (kg)
Dibucaine + saline solution	15	70 (54,76)	165 (162,171)	77 (67,87)
Dibucaine + epinephrine	15	69 (61,73)	164 (161,169)	73 (65,82)

Table 2. Duration of Spinal Anaesthesia

Group	Median two segment regression time (min)	Median L-1 regression time (min)
Dibucaine + saline solution	90	180
Dibucaine + epinephrine	120	255
Median of the differences (95% confidence interval group 2 − group 1)	45 (0,90)	60 (30,120)
P	<0.05	<0.001

Table 3. Median Thoracic Dermatome Level over First 75 Minutes

	Time since commencement of block (min)							
	5	10	15	20	30	45	60	75
Dibucaine + saline solution	12	9	8	7	7	7	9	9
Dibucaine + epinephrine	10	8	6	6	5	7	5	6
Median of the difference	1	1	1	1	1	1	2	2
95% confidence interval	0,3	−2,3	−1,3	−1,3	−1,3	−1,4	0,5	0,5
P >	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

Table 4. Pharmacological Support of Circulation and Operation Site

Group	Vasopressor required		Operative site		
	Yes	No	Hip	Knee	Foot
Dibucaine + saline solution	4	11	6	6	3
Dibucaine + epinephrine	6	9[a]	8	4	3[a]

[a] $P > 0.05$.

Statistical analysis was performed by the Minitab statistical package (9) on a personal computer, with use of the Mann-Whitney and χ^2 tests as appropriate. Differences were considered significant when $P < 0.05$.

Results

Thirty-five patients were entered into the study. Four patients were excluded from analysis because of inadequate levels of anesthesia (two from the saline solution group, two from the group receiving epinephrine) and one was excluded because extensive blockade required intubation and ventilation to maintain satisfactory respiratory status (epinephrine group). A total of 15 patients in each group completed the study. The groups were comparable in terms of age, weight, and height (Table 1). The time taken for anesthesia to regress two segments and to regress to below the 12th thoracic dermatome was significantly increased in those patients given epinephrine (Table 2). There was no statistically significant difference in the median height of the block over the first 75 min between those patients given epinephrine compared with those given normal saline solution (Table 3). The median maximal height of the block in the group receiving epinephrine (T-5), one dermatome level higher compared with the group receiving saline solution (T-6), was not statistically significant (95% confidence interval of the difference 0.00, 4.00; $P > 0.05$). The need for pharmacological support of the circulation was similar in the two groups (Table 4). There were no long-term complications stemming from the spinal anesthetic.

Discussion

This study confirms reports (7,8) that the addition of 200 μg of epinephrine to 0.5% hyperbaric dibucaine significantly prolongs the duration of spinal anesthesia.

Vasoconstriction of subarachnoid vessels is unlikely to be the mechanism by which epinephrine prolongs the duration of some local anesthetics injected into the subarachnoid space. This is because no difference exists between the absorption rates of plain and epinephrine containing solutions of either lidocaine (10) or tetracaine (11). Direct neural action now appears to be responsible for the prolongation of spinal blockade by α-agonists. Collins et al. (12) demonstrated that the spinal administration of epinephrine in spinal cord transected decerebrate cats significantly reduced, in a dose-dependent manner, noxiously induced activity in a group of neurons involved in the central transmission of information about pain. The α_2-agonist clonidine exerts an analgetic effect after intrathecal administration, which can be antagonized by the α-antagonist phentolamine (13). Clonidine also prolongs the duration of local anesthetics administered to the subarachnoid space in both animals (14) and humans (15).

Goto et al. (16) recently reported the clinical prolongation of 0.3% hyperbaric dibucaine spinal anesthesia with very low doses of catecholamines: 2.5 μg epinephrine prolonged the time to two segment regression of anesthesia from 96 to 136 min, a similar dose of norepinephrine resulted in prolongation of anesthesia to 193 min. Unfortunately, there are several methodological problems in their study: data from patients receiving widely varying doses of catecholamine were pooled to determine the average maximal height of block, and the number of patients excluded from analysis is not detailed. The statistical method chosen to analyze the data from a small sample size was not mentioned; nonparametric tests are probably the most appropriate ones to use in such a study (17). Their claim that norepinephrine prolonged the duration of anesthesia more than epinephrine was not supported by statistical analysis. The patients in the study of Goto et al. (16) were younger, considerably lighter (average weight 54 kg), and probably shorter than those in the present study, differences that are known to alter the duration of spinal anesthesia (18,19). It is unlikely, however, that these factors fully account for the reported 50–100% increase in duration of anesthesia with use of catecholamine doses one-eightieth of those used routinely to achieve a 25% prolongation of spinal anesthesia. The final conclusion of Goto et al. (16) that ischemic damage to the spinal cord may be caused by abnormally high levels of CSF catecholamines during spinal anesthesia is unsubstantiated by either their own study or by the absence of reports of catecholamine-induced spinal cord ischemia despite the current clinical practice employing subarachnoid catecholamine doses several orders of magnitude greater than those employed by Goto et al. (16).

In conclusion, 200 μg of epinephrine added to 0.5% hyperbaric dibucaine led to a 30% prolongation of spinal anesthesia in an elderly population undergoing major lower limb orthopedic surgery, without altering the requirement for vasopressor administration.

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References

1. Chambers WA, Littlewood DG, Scott DB. Spinal anaesthesia with hyperbaric bupivacaine. Effect of added vasoconstrictors. Anesth Analg 1982;61:49–52.
2. Moore DC. Spinal anesthesia: bupivacaine compared with tetracaine. Anesth Analg 1980;59:743–50.
3. Chambers WA, Littlewood DG, Logan MR, Scott DB. Effect of added epinephrine on spinal anesthesia with lidocaine. Anesth Analg 1981;60:417–20.
4. Leicht CH, Carlson SA. Prolongation of lidocaine spinal anesthesia with epinephrine and phenylephrine. Anesth Analg 1986;65:365–9.
5. Egbert LD, Deas TC. Effect of epinephrine upon the duration of spinal anesthesia. Anesthesiology 1960;21:345–7.
6. Cummings GC, Bamber DB, Edstrom HH, Rubin AP. Subarachnoid block with bupivacaine. A comparison with cinchocaine. Br J Anaesth 1984;56:573–9.
7. Cousins MJ, Bridenbaugh PO. Neural blockade in clinical anesthesia and management of pain. 2nd ed. Philadelphia: J.B. Lippincott, 1988:222–3.
8. Cook PT, Davies MJ, Cronin KD, Moran P. A prospective randomised trial comparing spinal anaesthesia using hyperbaric cinchocaine with general anaesthesia for lower limb vascular surgery. Anaesth Intensive Care 1986;14:373–80.
9. Ryan BF, Joiner BL, Ryan TA. Minitab handbook. 2nd ed. Boston: Duxbury Press, 1985:260–99.
10. Denson DD, Bridenbaugh PO, Turner PA, Phero JC, Raj PP. Neural blockade and pharmacokinetics following subarachnoid lidocaine in the rhesus monkey. 1. Effects of epinephrine. Anesth Analg 1982;61:746–50.
11. Converse JG, Landmesser CM, Harmel MH. The concentration of pontocaine hydrochloride in the cerebrospinal fluid during spinal anesthesia, and the influence of epinephrine in prolonging the sensory anesthetic effect. Anesthesiology 1954;15:1–10.
12. Collins JG, Kitahata LM, Matsumoto M, Homma E, Suzukawa M. Spinally administered epinephrine suppresses noxiously evoked activity of WDR neurones in the dorsal horn of the spinal cord. Anesthesiology 1984;60:269–75.
13. Yaksh TL, Reddy SVR. Studies in the primate on the analgetic effects associated with intrathecal action of opiates, alpha adrenergic agonists and baclofen. Anesthesiology 1981; 54:451–67.
14. Bedder MD, Kozody R, Falahniuk MD, Cumming MO, Pucci WR. Clonidine prolongs tetracaine spinal anesthesia in dogs. Anesth Analg 1986;65:S14.
15. Racle JP, Benkhadra A, Poy JY, Gleizal B. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg 1987; 66:442–6.
16. Goto F, Fujita N, Fujita T. Cerebrospinal fluid catecholamine levels and duration of spinal anaesthesia. Can J Anaesth 1988;35:157–61.
17. Bourke GJ, Daly LE, McGilvray J. Interpretation and uses of medical statistics. 3rd ed. Oxford: Blackwell Scientific Publications, 1985:98.
18. Racle JP, Benkhadra A, Poy JY, Gleizal B. Spinal analgesia with hyperbaric bupivacaine: influence of age. Br J Anaesth 1988; 60:508–14.
19. McCulloch WJD, Littlewood DG. Influence of obesity on spinal analgesia with isobaric bupivacaine. Br J Anaesth 1986; 58:610–4.

Adverse Responses Following Intraoperative Administration of Orthoclone OKT3

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Key Words: SURGERY, TRANSPLANTATION—kidney, orthoclone. KIDNEY, TRANSPLANTATION—orthoclone.

The efficacy of orthoclone OKT3 (Muromonab CD3, Ortho Pharmaceutical, Raritan, N.J.) in the prevention and treatment of renal transplant rejection has been demonstrated (1,2). Its effectiveness is related to suppression of T-lymphocyte activity. Adverse reactions to OKT3, typically occurring during the administration of the first dose, have been reported and most commonly include fever, chills, headache, nausea and vomiting, tachycardia, and hypertension. Less frequent reactions include seizures and aseptic meningitis (1–3). Previous reports have described reactions without specific reference to adverse sequelae in anesthetized patients. As some of the signs and symptoms of the reaction may be masked under anesthesia, only severe manifestations of intraoperative toxicity may be evident. The purpose of this series of case reports is to alert anesthesiologists to the nature of adverse reactions to OKT3 that may occur intraoperatively.

Case 1

A 39-yr-old, 57-kg woman with chronic renal failure underwent cadaveric renal transplantation. Preoperative blood pressure (BP) was 130/70 mm Hg; heart rate was 80 beats/min. Levels of serum electrolytes were within normal limits except for elevations in blood urea nitrogen (BUN) and creatinine. Phenytoin 1 g was administered intravenously over the 1-h period before induction of anesthesia as prophylaxis against OKT3-induced seizures. Anesthesia was induced with thiamylal 150 mg, fentanyl 100 μg, and vecuronium 6 mg and was maintained with fentanyl 50 μg/h, 50% nitrous oxide (N_2O)–50% oxygen (O_2) and isoflurane, approximately 0.5% inspired concentration. Approximately 2 h after induction, OKT3 10 mg was administered intravenously over 3 min. Five minutes later the heart rate decreased to 40 beats/min and rapidly progressed to complete atrioventricular block, despite treatment with 5 mg of ephedrine and 0.8 mg of atropine. External chest compression was begun and continued for approximately 1 min; 100 μg epinephrine was given intravenously, resulting in restoration of normal sinus rhythm at a rate of 90 beats/min and a BP of 100/50 mm Hg. An arterial blood sample drawn during resuscitation showed pH 7.26, Pco_2 28 mm Hg, and Po_2 122 mm Hg. The operation was completed 2 h later, and the patient's postoperative course was notable for a urine output of 2 to 3 mL/h and decreased arterial Po_2 (83 mm Hg breathing 50% O_2). Physical examination and chest roentgenographic appearance were consistent with pulmonary edema. A pulmonary artery catheter showed a pulmonary artery pressure of 40/18 mm Hg and pulmonary capillary wedge pressure of 8 mm Hg. Positive pressure ventilation was continued for 8 h postoperatively, and hemodialysis was performed as well. After this, oxygenation improved and mechanical ventilation was discontinued. The patient made a full recovery and was discharged with a functioning renal transplant on the seventh postoperative day.

Case 2

A 30-yr-old, 51-kg woman with chronic renal failure underwent cadaveric renal transplantation. Serum levels of electrolytes were within normal limits but BUN and creatinine were elevated. Preoperatively, arterial BP (measured with a radial arterial catheter) was 170/100 mm Hg and heart rate 100 beats/min. Anesthesia was induced with thiamylal 325 mg, fentanyl 250 μg, and atracurium 30 mg and maintained

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with 50% N_2O–50% O_2, fentanyl (intermittent 50 μg boluses), and isoflurane 0.5 to 1.5% inspired concentration. Approximately 45 min after induction, phenytoin 1 g was given intravenously over 30 min. OKT3 10 mg was then administered as a rapid intravenous (IV) bolus within 10 min after the completion of the phenytoin infusion. Approximately 10 min later, arterial BP declined from 130/70 mm Hg to 75/40 mm Hg, heart rate decreased from 110 to 100 beats/min, and arterial hemoglobin saturation (measured with a pulse oximeter) decreased from 98 to 85%. Arterial blood gas tensions were not measured at the time. The decreases in BP and O_2 saturation were treated with O_2, 100%, and ephedrine, 5 mg IV. An arterial blood sample obtained 30 min later with the patient breathing 100% O_2 had a pH of 7.41, P_{CO_2} of 35 mm Hg, and P_{O_2} of 399 mm Hg. The remainder of the intraoperative course was uneventful, and O_2 saturation subsequently remained at 100% with the patient again breathing 50% O_2.

Case 3

A 22-yr-old, 52-kg woman underwent repeat cadaveric renal transplantation for a failed transplantation. Serum levels of electrolytes were within normal limits. Anesthesia was induced with thiamylal 400 mg, fentanyl 150 μg, and atracurium 40 mg intravenously and subsequently maintained with intermittent boluses of fentanyl, 50% N_2O–50% O_2, and isoflurane, 0.5 to 0.75% inspired concentration. OKT3 10 mg was given intravenously over 15 min 1 h after induction. No phenytoin was administered. Approximately 1 h later, arterial BP declined to 70/40 mm Hg without a change in heart rate. Simultaneously, O_2 saturation measured with a pulse oximeter decreased from 96 to 91%. Blood gas tensions were not measured. Both changes resolved within 1 to 2 min after the administration of 5 mg ephedrine and the addition of 5 cm PEEP to the breathing circuit. The remainder of the operative course was uneventful.

Case 4

A 51-yr-old, 53-kg woman underwent cadaveric renal transplantation. Preoperative history was notable for hypertension and indications of left ventricular hypertrophy on the electrocardiogram. Serum levels of electrolytes were within normal limits. Preoperative medications included nifedipine, 20 mg four times a day, and atenolol, 50 mg twice a day. Anesthesia was induced with midazolam 7 mg, fentanyl 250 μg, and atracurium 25 mg intravenously and maintained with isoflurane 1.5% inspired and 50% N_2O–50% O_2. An infusion of OKT3 was begun 30 min after induction, and 5 mg was infused over 30 min. At the end of that time, the heart rate abruptly decreased from 62 to 40 beats/min and the arterial BP declined from 150/70 to 120/60 mm Hg. Oxygen saturation remained at 100%. Atropine 0.6 mg was given intravenously, resulting in an increase in heart rate and BP to the values present before administration of OKT3. An additional 5 mg of OKT3 was given without incident. The remainder of the procedure was uneventful.

Discussion

Acute rejection of the allograft remains a major clinical problem in renal transplantation. Conventional therapy for rejection has included high-dose steroids and antithymocyte globulins. Monoclonal antibodies directed against a specific target or antigenic determinant have been available since 1975 (4). OKT3 is the first monoclonal antibody approved for therapeutic use. It is prepared by immunizing mice against human peripheral T lymphocytes. OKT3 is a murine monoclonal IgG2a antibody that reacts specifically with the 20,000 dalton CD3, or T3 molecular complex of T cells (1). T cells are involved in the cellular immune responses that are responsible for rejection. The T3 region on the T-cell membrane consists of polypeptide chains that relay signals to T cells after antigen recognition (5). These signals activate the T cell to release interleukin 2, which in turn stimulates cytotoxic T cells to react to the foreign antigen (in this instance the renal allograft). Only T cells are affected by OKT3. After OKT3 occupies the receptor site on the T3 complex, host T cells lose their ability to react to foreign antigens. In vitro, OKT3 blocks killing by cytotoxic human T cells and blocks the generation of other T-cell functions. All T cells react with OKT3; this results in their removal from the circulation within 1 h after OKT3 is administered (6). Complement is not involved in this reaction; rather, opsonized T cells are removed by the reticuloendothelial system in the liver or spleen. Within 24 to 48 h after OKT3 administration is stopped, T-cell function returns.

The Ortho Multicenter Transplant Study, a randomized trial of 123 patients undergoing acute rejection of renal allografts, demonstrated that 94% of rejection episodes were reversed with OKT3, a significantly better success rate than the 75% achieved with conventional steroid use (1). Studies of OKT3 for prophylaxis against rejection are in progress; to date they have shown an effectiveness similar to that obtained with conventional immunosuppressive agents (2,7). Therefore, it seems likely that its use at the time of transplantation will increase.

Adverse reactions to OKT3 are frequent following the first dose. In the OKT3 multicenter trial, reactions were noted as follows: 73% of the patients developed pyrexia, 57% chills, 10% tremor, 21% dyspnea, 14% chest pain and tightness, 11% wheezing, 11% nausea, and 13% vomiting. The reactions typically occurred 45 to 60 min after the dose was administered and lasted for several hours. The use of acetaminophen, diphenhydramine, and corticosteroids prior to or at the time of administration of OKT3 decreased but did not eliminate the occurrence of reactions (1). Slow IV infusion did not reduce symptoms. Pulmonary edema also occurred in a small number of patients. In 122 patients receiving their first dose of OKT3 for prophylaxis, Thistlethwaite et al. reported a 64% incidence of hypertension and an 18% incidence of hypotension. Aseptic meningitis or seizures occurred in about 15% (2). The incidence of reactions is lower with multiple exposures. In the same report the first dose was given during the transplantation procedure, but the authors did not describe the specific nature of any serious intraoperative reactions such as hypotension. Their dose of OKT3 was limited to 5 mg/day. In the Ortho Multicenter Trial, OKT3 was given to awake patients.

OKT3 itself is not intrinsically harmful to the heart and lungs. The hypotension and arterial desaturation we have seen following its use are most likely the result of subsequent immune reactions (8). Binding of OKT3 to the T3 receptor on T cells leads to two major responses. First, the T cells are stimulated to produce various cytokines. These polypeptides are chemoattractants for polymorphonuclear and mononuclear leukocytes and, in addition, stimulate these cells to produce leukotrienes (peptidyl and nonpeptidyl), prostaglandins, thromboxanes, and prostacyclins (9). The second major response to the binding of OKT3 to T lymphocytes is their destruction by the reticuloendothelial system. This leads to a further increase in the levels of mediators and arachidonic acid metabolites in the circulation as the contents of the disintegrating T cells are released.

Leukotrienes may produce severe decreases in cardiac contractility and may also produce coronary artery vasospasm (10,11), the basis for the phenomenon known as "cardiac anaphylaxis." The "E" series prostaglandins and prostacyclins could produce a concomitant decrease in systemic vascular resistance (12). In the lung, "F" series prostaglandins and leukotrienes may cause pulmonary hypertension, leading to increased fluid transudation into the pulmonary interstitium and alveoli (13). Prostanoids may directly increase the permeability of pulmonary vascular endothelium or attract leukocytes and platelets that themselves injure the endothelium and alter permeability (14). Thus, the net effect of these mediators on the heart and lungs would be expected to consist of hypotension and arterial desaturation as experienced by the patients in our report.

The time course of adverse reactions after OKT3 administration varied in our patients from immediately after administration to nearly 1 h later. In previous reports of reactions (1,3), the usual time course was 30 to 60 min after OKT3 infusion. This time course is consistent with the reactions in patients 3 and 4 but may not be in patients 1 and 2. Reasons for this discrepancy include the following: 1) in both patients, 10 mg, or twice the previously described dose, was used; 2) both patients received phenytoin prior to OKT3, which may have produced additive cardiovascular depression; 3) in previous studies, monitoring may not have been as intense as in an anesthetized patient, resulting in later recognition. Due to the confounding effects of a large number of drugs received in the perioperative period, surgical manipulation, and other physiological disturbances possible in the perioperative period, we cannot establish with complete certainty a direct cause and effect relationship between OKT3 and the reactions observed in our four patients. Nevertheless, the anesthesiologist would be well advised to be prepared to treat similar disturbances in patients receiving OKT3 intraoperatively.

Most patients who receive OKT3 do not experience hypotension or arterial desaturation. Our experience leads us to believe that the following factors increase the likelihood of these types of severe acute reactions to OKT3: high dose (on a mg/kg basis), concomitant administration of drugs that decrease cardiac contractility, e.g., phenytoin, β-blockers, calcium channel blockers, volatile anesthetic agents, and hypovolemia. We believe that appropriate treatment of such reactions should include discontinuing the use of negative inotropic agents, IV fluid resuscitation, positive pressure mechanical ventilation with PEEP, and, in extreme cases, inotropic and vasopressor agents.

References

1. Ortho Multicenter Transplant Group. A randomized clinical trial of OKT3 monoclonal antibody for acute rejection of cadaveric renal transplants. N Engl J Med 1985;313:337–42.
2. Debure A, Chkoff N, Chatenoud L, et al. One month prophylactic use of OKT3 in cadaver kidney transplant recipients. Transplantation 1988;45:546–53.

3. Thistlethwaite JR, Stuart JK, Mayes JT, et al. Monitoring and complications of monoclonal therapy: complications and monitoring of OKT3 therapy. Am J Kidney Dis 1988;11:112–9.
4. Emmons C, Hunsicker LG. Muromonab-CD3 (Orthoclone OKT3): The first monoclonal antibody approved for therapeutic use. Iowa Med 1987;77:78–82.
5. Reinherz EL, Meuer S, Fitzgerald KA, et al. Antigen recognition by human T lymphocytes is linked to surface expression of the T3 molecular complex. Cell 1982;30:735–43.
6. Canafax DM, Draxler CA. Monoclonal antilymphocyte antibody (OKT3) treatment of acute renal allograft rejection. Pharmacotherapy 1987;7:121–4.
7. Norman DJ, Shield CF, Barry J, et al. Early use of OKT3 monoclonal antibody in renal transplantation to prevent rejection. Am J Kidney Dis 1988;11:107–10.
8. Thistlethwaite JR, Cosimi AB, Delmonico FL, et al. Evolving use of OKT3 monoclonal antibody for treatment of renal allograft rejection. Transplantation 1984;38:695–701.
9. Tsai JJ, Maestrelli P, Cromwell O, et al. A T-lymphocyte-derived factor that enhances IgG-dependent release of leukotriene B4 (LTB4) from human neutrophils. Immunology 1988; 65:449–56.
10. Burke JA, Levi R, Guo ZG, et al. Leukotrienes C4, D4, and E4: Effects on human and guinea-pig cardiac preparations in vitro. J Pharmacol Exp Ther 1982;221:235–41.
11. Ezra D, Boyd LM, Feuerstein G, et al. Coronary vasoconstriction by leukotriene C4, D4, and E4 in the intact pig heart. Am J Cardiol 1983;51:1451–4.
12. Meyrick B, Hoover R, Jones MR, et al. In vitro effects of endotoxin on bovine and sheep lung microvascular and pulmonary artery endothelial cells. J Cell Physiol 1989;138:165–74.
13. Lee CW, Jung W, Lewis RA, Hales C. LBT4 mediated hypoxemia in guinea pigs: relationship to pulmonary and cardiovascular pathophysiology. Prostaglandins 1987;33:3–16.
14. Morganroth ML, Till GO, Schoeneich S, Ward PA. Eicosanoids are involved in the permeability changes but not the pulmonary hypertension after systemic activation of complement. Lab Invest 1988;58:316–23.

826 ANESTH ANALG
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Epidural Morphine Provides Greater Pain Relief Than Patient-Controlled Intravenous Morphine Following Cholecystectomy

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Key Words: ANALGESICS, MORPHINE. ANESTHETIC TECHNIQUES, EPIDURAL—morphine. PAIN, POSTOPERATIVE.

The management of postoperative pain today increasingly involves use of either epidural narcotics or intravenous (IV) patient-controlled analgesia (PCA) (1,2). Neither technique is without risk or undesirable side effects, such as pruritus, nausea, and urinary retention. Whereas epidural morphine requires vigilance to detect occasional respiratory depression (2), IV PCA requires expensive delivery systems subject to mechanical failure or human error (3).

The few studies that have compared epidural to IV PCA morphine for the management of postoperative pain are limited because only a single dose of epidural narcotic was administered (4–6). Following lower extremity surgery, we found that epidural morphine provided greater patient comfort both at rest and with ambulation (7). Epidural morphine may thus be particularly advantageous to facilitate early joint mobilization.

Postoperative pain following upper abdominal surgery is often increased with coughing. This effect may cause splinting and a reluctance to breathe deeply (8). The purpose of this report is to evaluate both the quality of analgesia and the incidence of side effects resulting from the management of postoperative pain with either epidural or IV PCA morphine in patients following cholecystectomy.

Methods

With the approval of the institutional human investigation committee, a prospective study was undertaken of 43 consecutive patients following cholecystectomy using a subcostal incision. All pertinent information during the course of providing analgesia was recorded on specially designed patient-care forms, checked for completeness, entered in a computer database, and retrieved for analysis at a later time. All patients were ASA physical status I and II, and ranged in age from 18 to 84 yr old.

Patients receiving general anesthesia received IV PCA morphine for postoperative analgesia. Intravenous PCA was initiated with an incremental dose of 1 mg of morphine, a lockout interval of 8 min, and a 4-h maximum dose of 30 mg. If pain persisted the incremental dose was increased to 1.5 mg and/or the lockout period decreased to 6 min. Patients were instructed both before and after their surgery to use the PCA morphine as needed to achieve comfort both at rest and upon coughing.

When general/epidural anesthesia was used, analgesia was provided with preservative-free morphine, administered through a catheter at the L2–3 or L3–4 interspace. An initial morphine dose, 2 to 4 mg depending on age, was administered in the operating room approximately 1 h before the expected completion of surgery. Subsequent morphine doses and intervals between epidural injections were adjusted as needed for each patient to achieve comfort at rest and during coughing. The importance of achieving a level of comfort to allow hourly incentive spirometry was explained to both groups.

The following information was collected daily: 1) the 24-h morphine dose; 2) self-assessment by patients of their pain at rest and upon coughing using a 0 to 10 verbal analogue scale, 0 = "no pain" and 10 = "severe pain"; 3) the incidence and severity of pruri-

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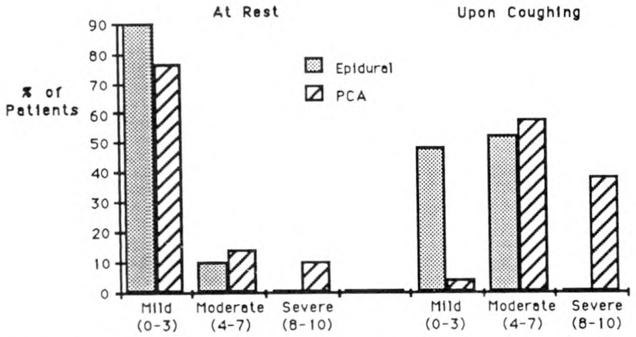

Figure 1. Distribution of pain scores. The pain scores on the first postoperative day were self-assessed by the patient using a 0 to 10 verbal analogue scale, 0 = "no pain" and 10 = "severe pain."

tus and nausea (0 = none; 1 = mild, no medical intervention; 2 = moderate, medications administered and effective; 3 = severe, medications administered but not effective); 4) the incidence and severity of urinary retention (0 = none; 1 = hesitancy; 2 = one or two bladder catheterizations needed; 3 = greater than two bladder catheterizations or a Foley catheter required); and 5) respiratory depression (respiratory rate < 8), as detected by a nurse at hourly checks.

Statistical analysis of categorical data (the incidence of side effects requiring medical intervention) was by the χ^2 test without correction for continuity. Continuous variables (age and verbal pain scores) were analyzed by the Mann–Whitney test. For statistical significance a two-tailed critical value of $P < 0.05$ was employed. Values are reported as mean ± standard deviation.

Results

Postoperative pain was managed with epidural morphine in 21 patients and with IV PCA morphine in 22 patients. There was no significant difference in the ages of the two groups (53 ± 18 and 45 ± 18 yr, respectively, $P = 0.23$).

Patients managed with epidural morphine reported significantly lower pain scores both at rest (0.8 ± 1.4 vs 2.7 ± 2.4, $P = 0.02$) and upon coughing (3.6 ± 2.1 vs 6.9 ± 2.1, $P = 0.0001$). Distributions of pain scores are shown in Figure 1. Though patients receiving epidural morphine had a significantly greater incidence of pruritus requiring medical intervention ($P = 0.02$), there were no significant differences with respect to the incidence of nausea or urinary retention (Figure 2). There was no clinically evident respiratory depression as assessed by respiratory rate.

Discussion

The effectiveness of incentive spirometry and early mobilization following upper abdominal procedures, currently so favored by surgeons for reduction of postoperative respiratory complications, may be limited by pain. Fewer postoperative pulmonary complications have been reported when analgesia reduces splinting and permits deep breathing, coughing, and chest physical therapy (8–10). Because pain is not static, but varies in accordance with patient activity, in the present study we distinguished between pain at rest and upon coughing. Epidural morphine provided greater pain relief under both circumstances than did IV PCA with morphine.

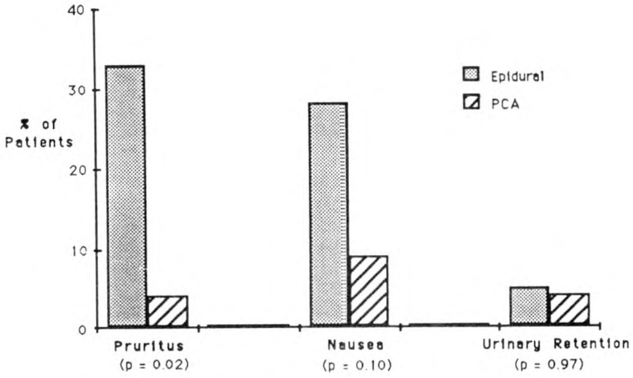

Figure 2. Incidence of side effects requiring medical intervention.

This design is nonrandomized and therefore subject to bias. We cannot be certain that the patients in the two groups had the same responses to pain. However, the observation that patients receiving morphine by an IV PCA system did not attain profound analgesia is in agreement with other studies (2,11). This may reflect the limitation imposed by increased side effects with the larger doses of IV narcotics needed for severe pain.

In summary we have shown that, compared to IV PCA morphine, epidural morphine provides greater patient comfort both at rest and upon coughing following upper abdominal surgery.

References

1. Vickers MD. Clinical trials of analgesic drugs. In: Harmer M, Rosen M, Vickers MD, eds. Patient-controlled analgesia. London: Blackwell, 1985:43.
2. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276–310.
3. White PF. Mishaps with patient-controlled analgesia. Anesthesiology 1987;66:81–3.
4. Eisenach JC, Grice SC, Dewan DM. Patient-controlled analgesia following cesarean section: a comparison with epidural and intramuscular narcotics. Anesthesiology 1988;68:444–8.
5. Harrison DM, Sinatra R, Morgese L, Chung JH. Epidural narcotic and patient-controlled analgesia for post-cesarean section pain relief. Anesthesiology 1988;68:454–7.
6. Hord AH. Comparing the efficacy of epidural opiates with that of patient-controlled analgesia. Anesthesiology 1988;69:632–3.

7. Loper KA, Ready LB. Epidural morphine following anterior cruciate ligament repair: a comparison with patient-controlled intravenous morphine. Anesth Analg 1989;68:350–2.
8. Rawal N, Sjöstrand U, Christoffersson E, et al. Comparison of intramuscular and epidural morphine of postoperative analgesia in the grossly obese: influence on postoperative ambulation and pulmonary function. Anesth Analg 1984;63:583–92.
9. Shulman M, Sandler AN, Bradley JW, Young PS, Brebner J. Postthoracotomy pain and pulmonary function following epidural and systemic morphine. Anesthesiology 1984;61:569–75.
10. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 1987;66:729–36.
11. Ferrante FM, Orav EJ, Rocco AG, Gallo J. A statistical model for pain in patient-controlled analgesia and conventional intramuscular opioid regimens. Anesth Analg 1988;67:457–61.

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Biphasic Carbon Dioxide Elimination Waveform with Right Mainstem Bronchial Intubation

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Key Words: CARBON DIOXIDE, CAPNOGRAPHY—biphasic waveform. ANESTHETIC TECHNIQUES, endobronchial.

The carbon dioxide (CO_2) elimination waveform is an accepted expression of the ventilation to perfusion relationship (V/Q). During initial exhalation, elimination of anatomical dead space (infinite V/Q, zero CO_2 concentration) is followed by elimination of well-ventilated, low-resistance regions of the lung (relatively high V/Q, low CO_2 concentration). Later, poorly ventilated, high-resistance regions of the lung (relatively low V/Q, high CO_2 concentration) are eliminated. The continuum of V/Q ratios between high and low V/Q areas creates a positive slope (upward to the right) to the alveolar plateau part (phase 3) of the CO_2 elimination waveform (1). Theoretically, if the continuum of V/Q ratios is broken into two distinctly different lung regions (a low-resistance, high-V/Q region and a high-resistance, low-V/Q region), a biphasic CO_2 excretion waveform might be expected. The only situations in which such a biphasic CO_2 waveform has been described are the lateral decubitus position (2) in which the nondependent lung has a relatively high V/Q ratio, low CO_2 concentration, and low airway resistance compared to the dependent lung (3), and in a supine patient with severe rotary kyphoscoliosis causing severe compression of one lung (4). We describe a patient in the supine position with a large right shoulder roll and head turned 45° to the left, who had nearly a completely biphasic CO_2 elimination waveform and who, in addition, at the end of operation was found, by fiberoptic bronchoscopy, to have the tip of the endotracheal tube in the proximal right mainstem bronchus.

Report of a Case

A 58-yr-old, 72-kg, 175-cm man presented for a repeat right temporal craniotomy and clipping of a right middle cerebral artery aneurysm. Eleven days previously he had undergone uneventful craniotomy at another hospital for evacuation of an intracerebral hematoma detected by computerized tomography. The aneurysm was found at the time of this initial operation, and the patient was transferred to our institution for definitive surgery. Speech and mental activity were appropriate but slowed.

The patient had an 80-pack/yr smoking history, but denied any pulmonary disease and claimed no dyspnea with briskly walking 2 to 3 flat miles. Preoperatively, he was found to have normal airway anatomy and bilateral clear breath sounds with good symmetrical excursions. While breathing room air arterial pH was 7.44, Pa_{O_2} was 97 mm Hg, and Pa_{CO_2} was 42 mm Hg. Chest roentgenogram and electrocardiogram were normal.

Using local anesthesia, catheters were placed in two peripheral veins, in the right subclavian vein and in the left radial artery. Monitors included an electrocardiogram, a pulse oximeter, end tidal capnography, and a right adductor pollicus neuromuscular stimulator.

Anesthesia was induced with sufentanil 50 μg IV and thiamylal 125 mg IV, with vecuronium 10 mg IV to facilitate tracheal intubation. At direct laryngoscopy the vallecula was noted to be quite deep, requiring a Macintosh 3-blade placed entirely in the mouth so that the hinge of the blade was at the lips. An 8-mm ID endotracheal tube with a Murphy eye was passed under direct visualization until the cuff was entirely through the true vocal cords and the 24-cm mark was next to the anterior middle incisor. The cuff was inflated to a just-seal volume. Following intubation, the breath sounds were bilateral and equal, the CO_2 capnogram appeared normal (similar to Figure 2), and the tracheal tube was firmly taped in place. The patient was then turned to the left lateral decu-

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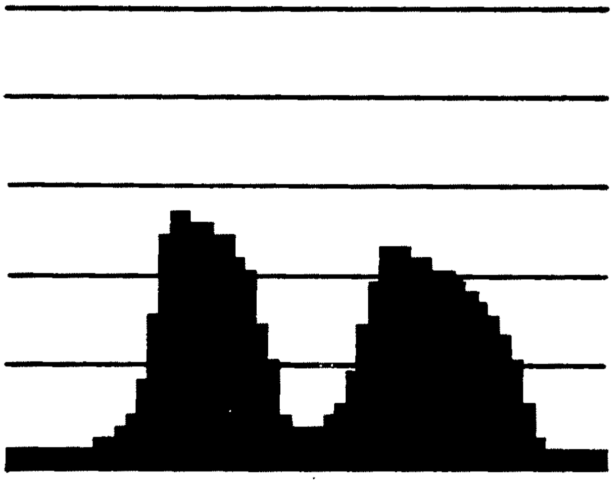

Figure 1. Biphasic capnogram during right mainstem bronchial intubation. Each *horizontal line* indicates 10 mm Hg CO_2 concentration. Read right to left. The first CO_2 concentration peak ranged from 21 to 23 mm Hg, and the second CO_2 concentration peak ranged from 26 to 29 mm Hg. No spontaneous ventilation was apparent during this period of controlled ventilation.

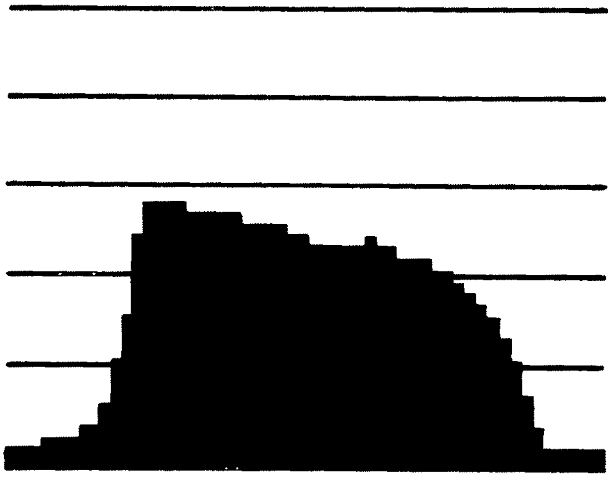

Figure 2. Normal appearing capnogram after the tip of the endotracheal tube was pulled back above the tracheal carina. Read right to left. Each *horizontal line* indicates 10 mm Hg CO_2 concentration; the end-tidal CO_2 concentration at the end of this breath was 28 mm Hg.

bitus position, at which time a lumbar subarachnoid drain was placed. The patient was returned to the supine position, and a right shoulder roll was placed by the surgeons. Sugita pins were then placed, requiring the patient's head to be turned 45° to the left in the head rest. After these maneuvers the breath sounds, endotracheal tube position, and capnogram were unchanged, and a humidifier was placed within the circuit. Positive pressure ventilation was controlled (Dräger 2 anesthesia machine) with a tidal volume of 1000 mL, rate 8/min, I:E ratio of 1:3, and fresh gas flow of 5 L/min, so that, for the entire subsequent course of anesthesia and surgery, peak inspiratory pressure was 30 cm H_2O, end tidal CO_2 concentration was 26 to 29 mm Hg, $Paco_2$ was 32 to 34 mm Hg, and Pao_2 was 155 to 196 mm Hg.

Anesthesia was maintained for 7.5 h with nitrous oxide 66%, a continuous infusion of sufentanil at 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$, and isoflurane 0.2 to 0.4%; relaxation was maintained with pancuronium 14 mg in seven equally divided doses. Throughout the entire induction and maintenance of anesthesia, systolic blood pressure ranged from 110 to 160 mm Hg, diastolic blood pressure from 65 to 90 mm Hg, pulse from 70 to 88 beats/min, and central venous pressure from 10 to 14 mm Hg.

Approximately 2 h into the operation, and without change in peak inspiratory pressure, an intermittent biphasic CO_2 waveform appeared on the capnograph and the presence of this biphasic waveform continued until the end of the procedure (Figure 1). The first peak of the biphasic waveform ranged from 21 to 23 mm Hg, whereas the second peak ranged from 26 to 29 mm Hg. The ventilating and CO_2 analyzer circuit integrity was thoroughly checked, and no leaks were detectable (5). Likewise, the one-way anesthesia circle system valves were functioning normally. A 14F suction catheter was easily passed down the full length of the endotracheal tube. Breath sounds were equal and clear bilaterally. To ensure that the patient was not attempting to breath spontaneously during controlled ventilation, multiple attempts were made to allow spontaneous ventilation. During these attempts, there was a complete absence of any neuromuscular twitch; no movement of the one-way anesthesia circle system valves, the chest, airway pressure manometer needle, and ventilator bellows; and there was no CO_2 on the capnograph. Similarly, no signs of spontaneous ventilation were apparent during the positive pressure breaths. The biphasic pattern was slightly diminished (smaller central cleft) by increasing the tidal volume (10–15%), increasing the I:E ratio (from 1:3.5 to 1:2.0), and increasing peak flow rates (uncalibrated dial on the Dräger 2). However, we were never able to make the waveform completely normal with any combination of these maneuvers.

Before awakening the patient and removing his head from the Sugita head rest, bronchoscopy was performed to determine the exact location of the tip of the endotracheal tube. It was found to lie in the right mainstem bronchus with the Murphy eye opposite the proximal margin of the right upper lobe bronchial orifice. As the endotracheal tube was slowly pulled back approximately 1 cm, the carina came into view. The capnograph then had a normal, continuously ascending plateau phase 3 (Figure 2).

The sufentanil infusion was discontinued 45 min before the conclusion of surgery. At the end of surgery, nitrous oxide and isoflurane were discontinued and the neuromuscular blockade reversed. The patient emerged from anesthesia with a spontaneous ventilatory rate of 14 breaths/min and was extubated uneventfully. On the first postoperative day his neurological examination had returned to the preoperative baseline. On the second postoperative day the patient was transferred back to the referring hospital.

Discussion

We observed a biphasic CO_2 elimination waveform in a patient with no known lung disease who was found to have a right mainstem bronchial intubation. The mainstem bronchial intubation, which most likely occurred at the time of the onset of the biphasic CO_2 elimination waveform, was probably facilitated by the head being turned to the left (6). We hypothesize that during inspiration and increasing positive pressure in the lungs (especially the right lung) with consequent lengthening of the tracheobronchial tree, the tip of the endotracheal tube probably backed out slightly, allowing near equal ventilation of both lungs. Thus, breath sounds and peak inspiratory pressure were not diagnostic of the mainstem bronchial intubation. During exhalation, decreasing positive pressure in the lungs, and shortening of the tracheobronchial tree, the tip of the endotracheal tube probably reentered the right mainstem bronchus. The fact that any maneuver that increased tidal volume (increased I:E ratio, peak flow rates, and tidal volume setting per se) slightly decreased the central cleft in the biphasic waveform was probably indicative of the fact that increased lung pressure was keeping the endotracheal tube out of the right mainstem bronchus for a slightly longer period of time. As the tip of the endotracheal tube was located in the proximal right mainstem bronchus, with all or most of the cuff presumably still lying within the tracheal lumen, we think it reasonable to assume that the initial lower CO_2 concentration peak of the biphasic waveform was from a better ventilated right lung.

There are two possible etiologies for the second slightly higher CO_2 concentration peak. First, reentry of the endotracheal tube into the right mainstem bronchus may have transiently delayed left lung emptying. Second, the reentry of the endotracheal tube into the right mainstem bronchus may have transiently blocked the right upper lobe. In either case (left lung or right upper lobe blockage), inhalation into either (or both) of these regions may have been initially impeded (the part of inhalation that occurred before the endotracheal tube backed out of the right mainstem bronchus), which caused the second peak to be slightly more elevated than the first. If we had been able to monitor only the end-tidal CO_2 concentrations with a mass spectrometer (not the waveform), we would probably have observed a simple small step increase (caused by the second peak) (7). We are certain that intermittent spontaneous inhalation (entrainment of CO_2 free air from the circuit) during respirator exhalation cycles did not cause the cleft between the peaks in the waveform. Upon partial removal of the endotracheal tube, so that the tip was in the lumen of the trachea, a normal capnogram was obtained.

We speculate that other pathophysiologic states that cause one whole lung (or lobe) to be significantly relatively hypoventilated due to a high airway resistance, and one whole lung to be normally ventilated due to a normal airway resistance, may also cause a biphasic CO_2 elimination waveform. Unilateral pathophysiologic states that might cause such a biphasic CO_2 elimination waveform pattern include obstruction of a mainstem bronchi (with a mass, secretions, external tumor, congenital stenosis, and/or endotracheal tube), and/or compression of a whole lung (by air, fluid, or blood).

Detection of a biphasic CO_2 elimination waveform may have diagnostic and therapeutic implications. Recognizing the biphasic waveform may initiate a search for, and eventual removal of, the cause of unilateral high airway resistance and hypoventilation. The removal of the cause may be effected by maneuvers such as withdrawal of the endotracheal tube (as demonstrated by this case), unilateral suctioning, bronchopulmonary lavage, chest drainage, among others.

In summary, we observed a biphasic CO_2 elimination waveform on capnography in a patient who had a bronchoscopically observed mainstem bronchial intubation and, most likely, had two lungs with distinctly different mechanics. The lungs most probably had different airway resistances and CO_2 concentrations resulting in a biphasic CO_2 elimination waveform. There are potentially other unilateral causes of such a biphasic CO_2 excretion waveform, and detection of a biphasic CO_2 excretion waveform may alert the observer to diagnose and treat a potentially dangerous, but reversible, unilateral pathophysiologic condition.

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Intraoperative Administration of the Intravenous Angiotensin-Converting Enzyme Inhibitor, Enalaprilat, in a Patient with Congestive Heart Failure

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Key Words: ENZYMES, ANGIOTENSIN CONVERTING—enalaprilat.

Patients with heart failure due to coronary artery disease can be managed by afterload reduction as long as myocardial oxygen consumption is not increased by tachycardia and coronary artery perfusion pressure is not compromised. Recently, angiotensin-converting enzyme (ACE) inhibitors have been introduced for this purpose, and the active form of the ACE inhibitor enalapril, enalaprilat, is now available in intravenous (IV) form. This report describes the intraoperative management of a patient with a history of heart failure and coronary occlusive disease who benefited dramatically from enalaprilat, as documented by both thermister-tipped pulmonary artery catheter monitoring and two-dimensional transesophageal echocardiography enhanced with color flow Doppler.

Case Report

The patient was a 66-yr-old, 95-kg, 177-cm man admitted for thoracic esophagogastrectomy for Barrett's esophagus with adenocarcinoma. Although he had never had anginal symptoms, previous work-up of a syncopal episode included a treadmill electrocardiogram (ECG) that was terminated after 4.5 min because of dyspnea, chest tightness, and diaphoresis. Maximal heart rate attained was 150 beats/min, with a blood pressure of 210/80 mm Hg. A thallium perfusion scan revealed apical, lateral, and high septal ischemic lesions. Coronary angiography demonstrated the following: (a) left main, 40% lesion; (b) left anterior descending, 75%–80% proximal lesion with sequential lesions leading to a 65% distal stenosis and a 60% ostial first diagonal lesion; (c) obtuse marginal, 90% proximal occlusion; and (d) right coronary (right dominant system) with a 99% distal lesion, involving the origins of the posterior descending and posterolateral branches. Ventriculography revealed a regional wall motion abnormality in the circumflex distribution; ejection fraction was estimated to be 35%. The patient also had a history of sustained ventricular tachycardia with persistence of occasional unifocal pulmonary venous capillaries (PVCs) treated with mexilitine (150 mg twice a day). Serum electrolyte levels, urinalysis, and blood count were normal. Pulmonary function tests showed mild restrictive and moderate obstructive disease with a good response to bronchodilators. A pulmonary artery catheter was placed on the day before surgery with the following pressure data (mm Hg): right atrium (RA) 10, right ventricle (RV) 60/3, pulmonary artery (PA) 58/25, pulmonary artery occlusion pressure (PaOP) 26, and thermodilution cardiac output 4.0 L/min. At that time treatment with IV nitroglycerin (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was started, with diminution of PA pressure to 22/14 mm Hg. A preoperative transthoracic echocardiogram was performed and, despite the difficulty of the study, confirmed poor left ventricle (LV) function and documented mitral regurgitation (MR). The presence of MR noted during transthoracic echocardiography suggests significant MR, but because of variability in patient anatomy as well as study technique, an absolute quantitation was not possible.

On the day of operation, the patient was premedicated with 0.1 mg/kg of morphine, and 0.3 mg of IM scopolamine, and was transported to the operating room breathing supplemental oxygen by nasal cannula. Electrocardiogram (leads II and V_5), digital

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pulse oximeter, and radial and pulmonary arterial pressure monitoring were established. Anesthesia was induced with 50 μg/kg of IV fentanyl and maintained with additional incremental fentanyl (5 μg/kg) and intermittent enflurane (0.25% inspired in oxygen). Muscle relaxation was provided with vecuronium (0.25 mg/kg IV). Induction was hemodynamically uneventful.

A two-dimensional transesophageal echocardiograph (2D-TEE) probe (Hewlett-Packard 77020 AC) was then placed atraumatically into the esophagus and the heart was interrogated. Anterior and posterior midpapillary to basilar hypokinesia and akinesia were noted, as well as some apical hypokinesia. Ejection fraction was calculated to be 35%. Color flow Doppler analysis revealed 4+ MR (Figures 1A, 2A) and negligible aortic insufficiency.

Pulmonary artery catheter monitoring revealed PA = 53/24 and PaOP = 23 mm Hg with a significant v-wave (15 mm) noted during PA occlusion. Blood pressure was 125/65 mm Hg. Cardiac output by both thermodilution and Doppler analysis was 3.6 L/min. One hour after incision the arterial pressure increased to 147/82 mm Hg, and PA pressure increased to 58/29 mm Hg, despite fentanyl (500 μg) administration and an increased rate of nitroglycerin infusion (2 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Heart rate was stable at 76 beats/min, without ST-segment change suggestive of ischemia. Cardiac output remained at 3.6 L/min. Interrogation with 2D-TEE revealed no new regional wall motion abnormality; MR remained at 4+, and ejection fraction was estimated at <30%. Enalaprilat (0.625 mg IV) was administered.

Within 3 min heart rate decreased to 68 beats/min (Figure 3), and PA and radial arterial pressures decreased to 42/15 and 110/55 mm Hg, respectively. Ten minutes after enalaprilat, cardiac output was 6.0 L/min by Doppler and 4.8 L/min by thermodilution. Mitral regurgitation at this time was less than 1+, and ejection fraction had increased to 47% (Figures 1B, 2B). Qualitatively, myocardial function was markedly improved. Thirty minutes after enalaprilat blood pressure was 105/55 mm Hg, PA was 22/08 mm Hg, PaOP was 7 mm Hg without v-wave, heart rate was 69 beats/min, and cardiac output 4.8 L/min. Urine output increased from 0.5 to 1.2 $mL \cdot kg^{-1} \cdot min^{-1}$.

The operation was completed uneventfully using a total fentanyl dose of 7.5 mg. Postoperatively the patient continued to receive IV enalaprilat, 0.625 mg every 6 h with stable cardiovascular parameters. He was gradually weaned from mechanical ventilation and extubated 22 h later. No postoperative change in his ECG occurred, and CPK-MB fractions were unchanged. He was discharged from the hospital on the 11th postoperative day.

Discussion

Afterload reduction in patients with LV failure is often effected using sodium nitroprusside or nitroglycerin, although reflex tachycardia may be a problem. Addition of a short-acting β-blocker to control heart rate may negate the beneficial increase in cardiac output obtained. Relying on inotropic agents may cause increases in myocardial oxygen demand that parallel increased ventricular performance.

Enalaprilat, the de-esterified product of the prodrug enalapril, is a biologically active ACE inhibitor presently available in parenteral form (1). Like its prototype drug, captopril, enalaprilat inhibits the enzyme that converts the inactive decapeptide angiotensin I to the active octapeptide angiotensin II. As angiotensin II is a potent vasoconstrictor, enalaprilat acts to relax vascular smooth muscle, thus providing the anesthesiologist with greater flexibility than has hitherto been available for the rapid treatment of LV failure.

It has been reported that the peak effect of enalaprilat is reached in 30 min (2). As demonstrated in our patient, however, salutary effects occurred within 2 min (Figure 3), with prompt reduction of both systemic and pulmonary vascular resistances. Concomitantly, cardiac index increased and all pulmonary arterial pressures, right atrial, and systemic arterial pressures decreased. For reasons not yet understood, heart rate is reported to remain the same or to decrease, as was the situation in our case. The result is an improvement in cardiovascular performance without an increase in myocardial oxygen demand. An increase in renal blood flow as a result of increased cardiac index has also been reported (3), perhaps manifested in this case by an increase in urine output.

The recommended initial dose of enalaprilat is 1.25–2.5 mg IV. At IV doses of 1.25, 2.5, 5.0, and 10.0 mg, no significant difference in hemodynamic effect has been demonstrated (4). Angiotensin II levels have been shown to decrease rapidly, with maximum suppression at 30 min and a duration greater than 90 min. Plasma renin activity increases dramatically (>300%) due to the loss of angiotensin II feedback; there is a progressive, time-delayed decrease in circulating plasma aldosterone levels. There is also considerable variability in neurohumoral response to ACE inhibitors, emphasizing the fact that the activity

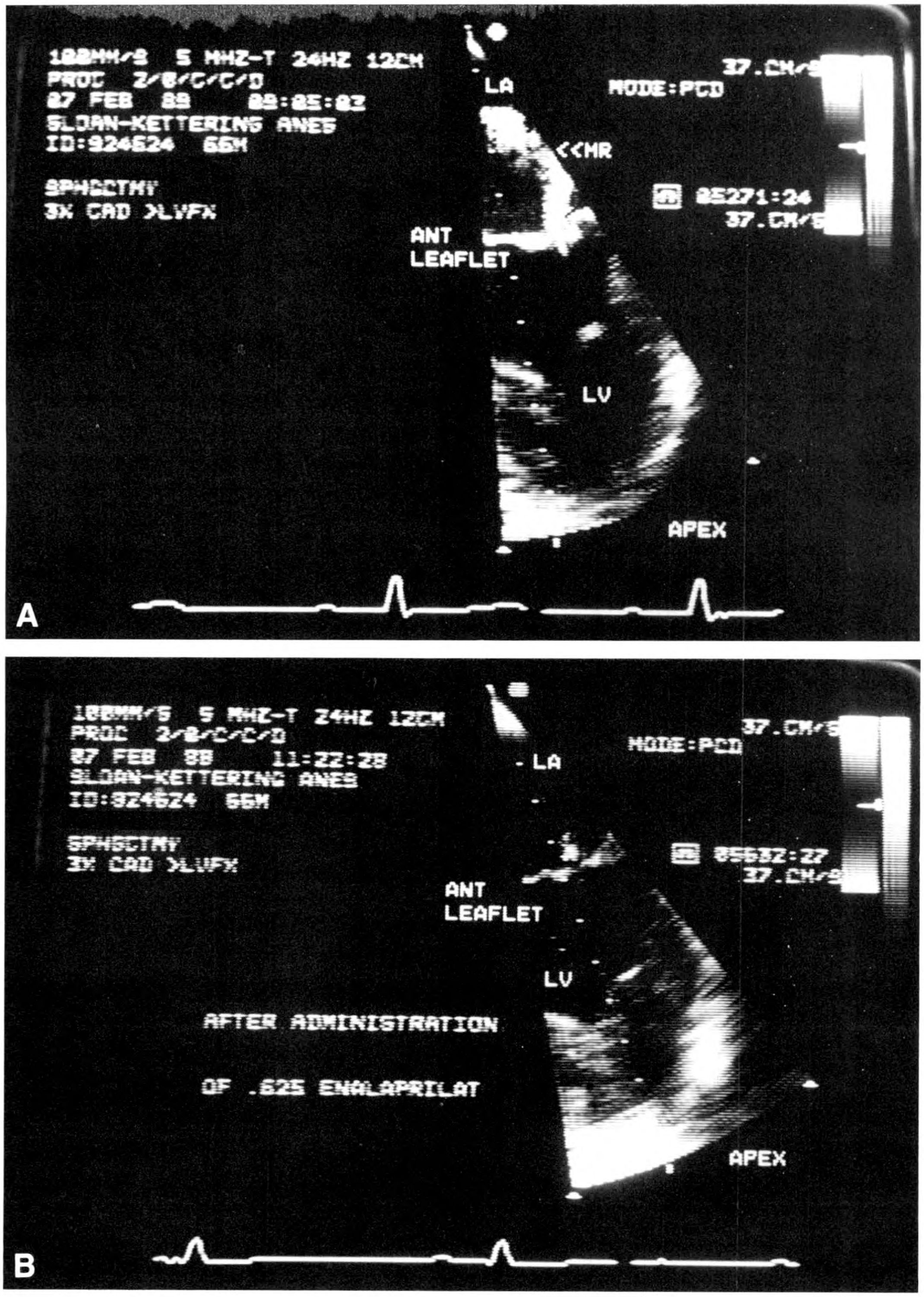

Figure 1. Long axis 2D-TEE view of the left ventricle with color flow Doppler analysis. Structures from top to bottom are, sequentially, left atrium (LA), mitral valve leaflets (anterior leaflet on left), and left ventricular cavity with LV septum on left and LV free wall on right. Both images are obtained 375 ms after onset of the QRS complex. The MR present at the beginning **(A)** is absent in the image obtained at 11:20 AM, 10 min after the administration of 0.625 mg of IV enalaprilat **(B)**.

of the renin-angiotensin system varies widely among patients with different degrees of congestive heart failure. A major response is often noted after an initial dose, due to simultaneous hemodynamic and neurohumoral effect. After an initial impact on the renin-angiotensin system, however, further enalapri-

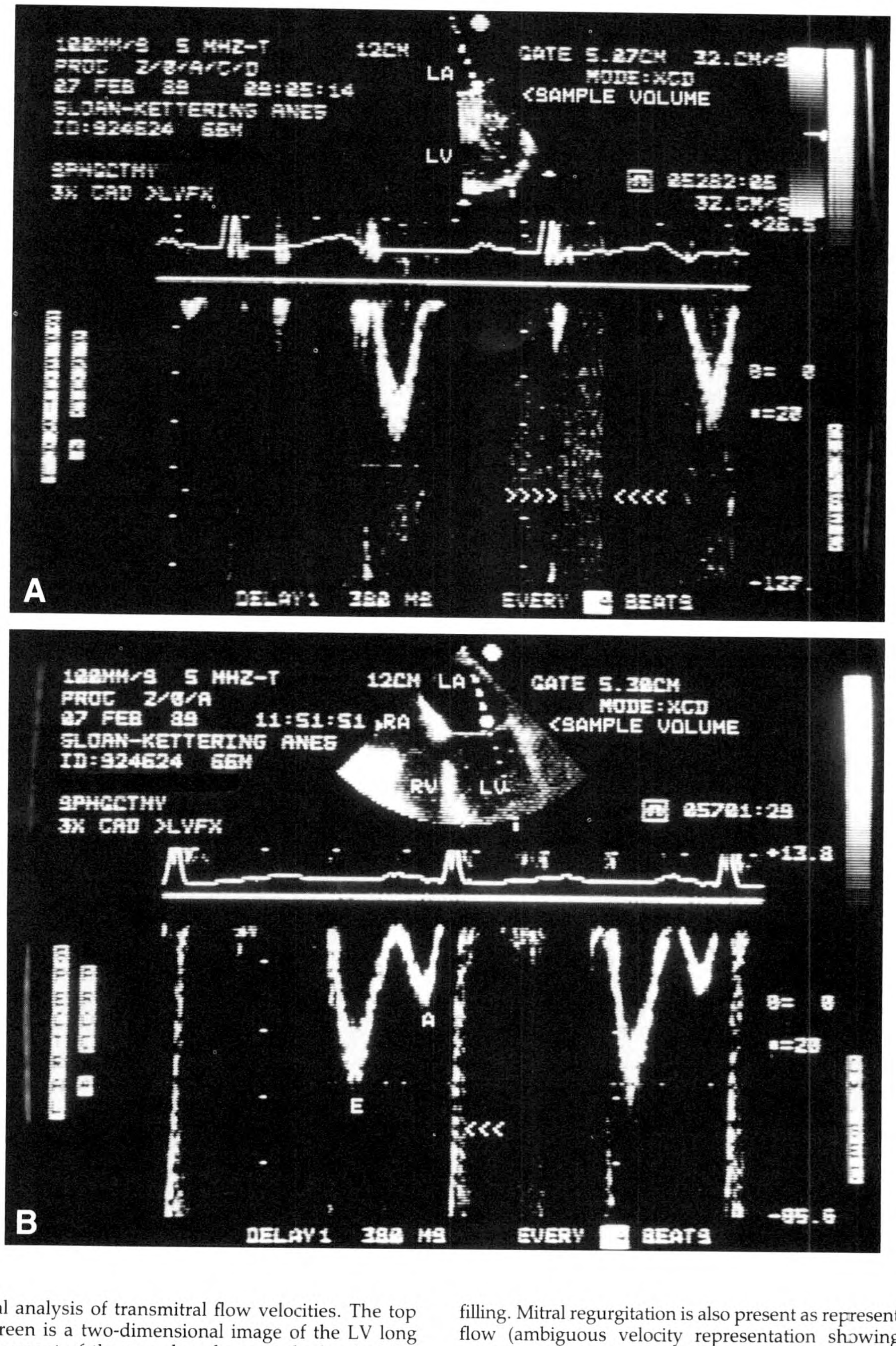

Figure 2. Spectral analysis of transmitral flow velocities. The top portion of the screen is a two-dimensional image of the LV long axis showing placement of the sample volume at the level of the mitral valve annulus. Spectral display (lower portion of the screen) shows ECG at top with zero baseline below. Velocity scale in centimeters per second is displayed to the right. Note that in the first frame **(A)**, there is a single inflow velocity occurring 440 ms after the onset of the QRS, and no measurable atrial contribution to filling. Mitral regurgitation is also present as represented by "aliased" flow (ambiguous velocity representation showing simultaneous positive and negative velocities) occurring at early systole (*between arrows*). At 11:51 **(B)** there is a normal 'E (ventricular component) and 'A (atrial component) velocity inscription during diastole with onset occurring 480 ms after the onset of the QRS. Note the absence of "aliased" flow during systole. (The sharp inscription occurring at the peak of R is coaptation of the mitral leaflet.)

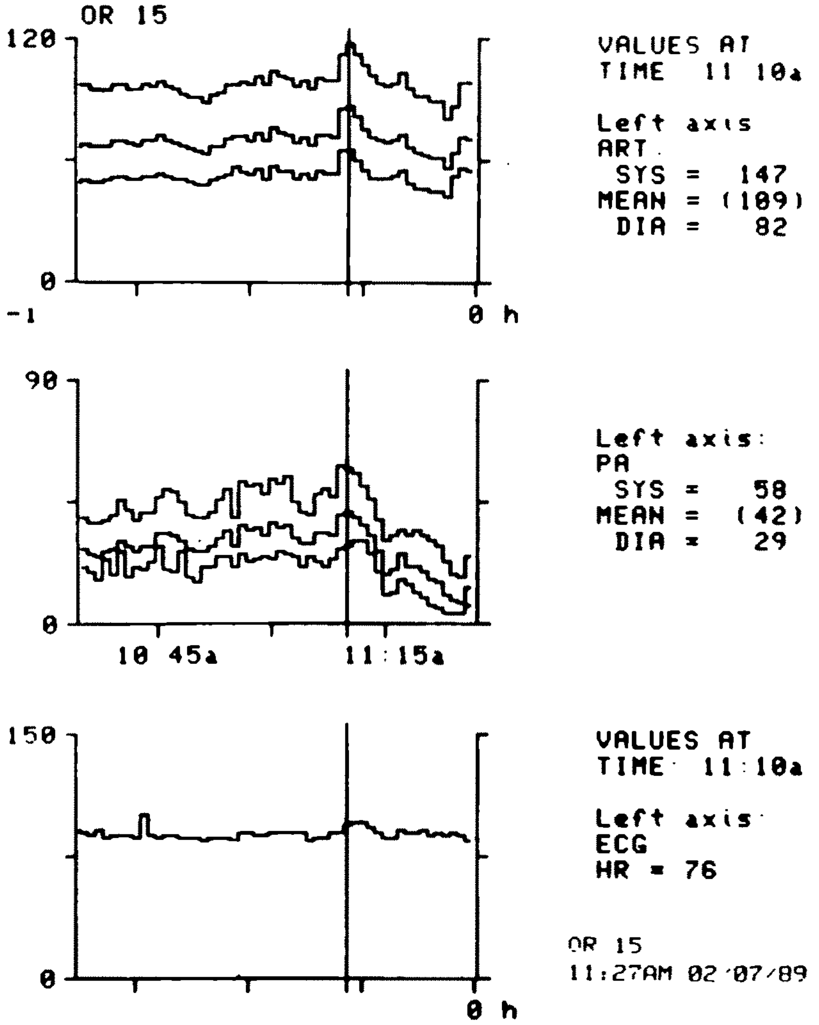

Figure 3. Graphic trend plot of arterial pressure, PA pressure, and heart rate. Enalaprilat (0.625 mg IV) was administered at 11:10 with vital signs at that time marked to the right of the graph. This trend persisted for the duration of the case. The central figure represents actuary time. It is vertically parallel to the apex and lower graphs, which represent time reversed from zero, at which time the recording was made. Vital signs at 12:38 were: BP, 104/54 mm Hg; PA, 24/10 mm Hg; and HR, 69 beats/min.

lat may result in much less dramatic hemodynamic effects. The mechanism by which a persistent salutary hemodynamic effect occurs with repeat doses remains to be elucidated. Once treatment with intravenous ACE inhibitors has been initiated, conversion to oral form can be effected simply by substitution of enalapril for enalaprilat.

The hemodynamic and neurohumoral effects of enalaprilat lend themselves to several intraoperative anesthetic applications. Patients with either chronic or borderline heart failure preoperatively, and who develop acute decompensation intraoperatively, have been shown to benefit from both short- and long-term afterload reduction (5). The direct reduction of systemic vascular resistance and peripheral vascular resistance is moderate, and, in those few cases where a more profound reduction occurs, blood pressure responds to fluid administration. Moreover, in patients with coronary occlusive disease, who cannot afford the increased oxygen demand associated with an increase in heart rate, the effect of ACE inhibitors on the baroreceptor-reflex is ideal. The use of ACE inhibitors in hypertensive patients with a high renin state is documented and logical, but ACE inhibitors have also been shown to benefit patients with congestive heart failure who do not have a high renin or sodium state (6). This latter response may be due to some other direct or indirect action of ACE inhibitors. Therefore, use of ACE inhibitors as an adjunct to anesthesia in patients with a history of hypertension may also be appropriate. To date, the use of ACE inhibitors in patients displaying right-sided heart failure remains to be studied, although it can be surmised that the direct reduction of PVR could be advantageous.

The successful treatment of MR in our patient demonstrates an additional effect of ACE inhibitors for patients with heart failure, coronary artery disease, and valvular insufficiency. As demonstrated in the hemodynamic data and the illustrations (Figures 1–4), the reduction in mitral insufficiency contributed significantly to the documented improvement in car-

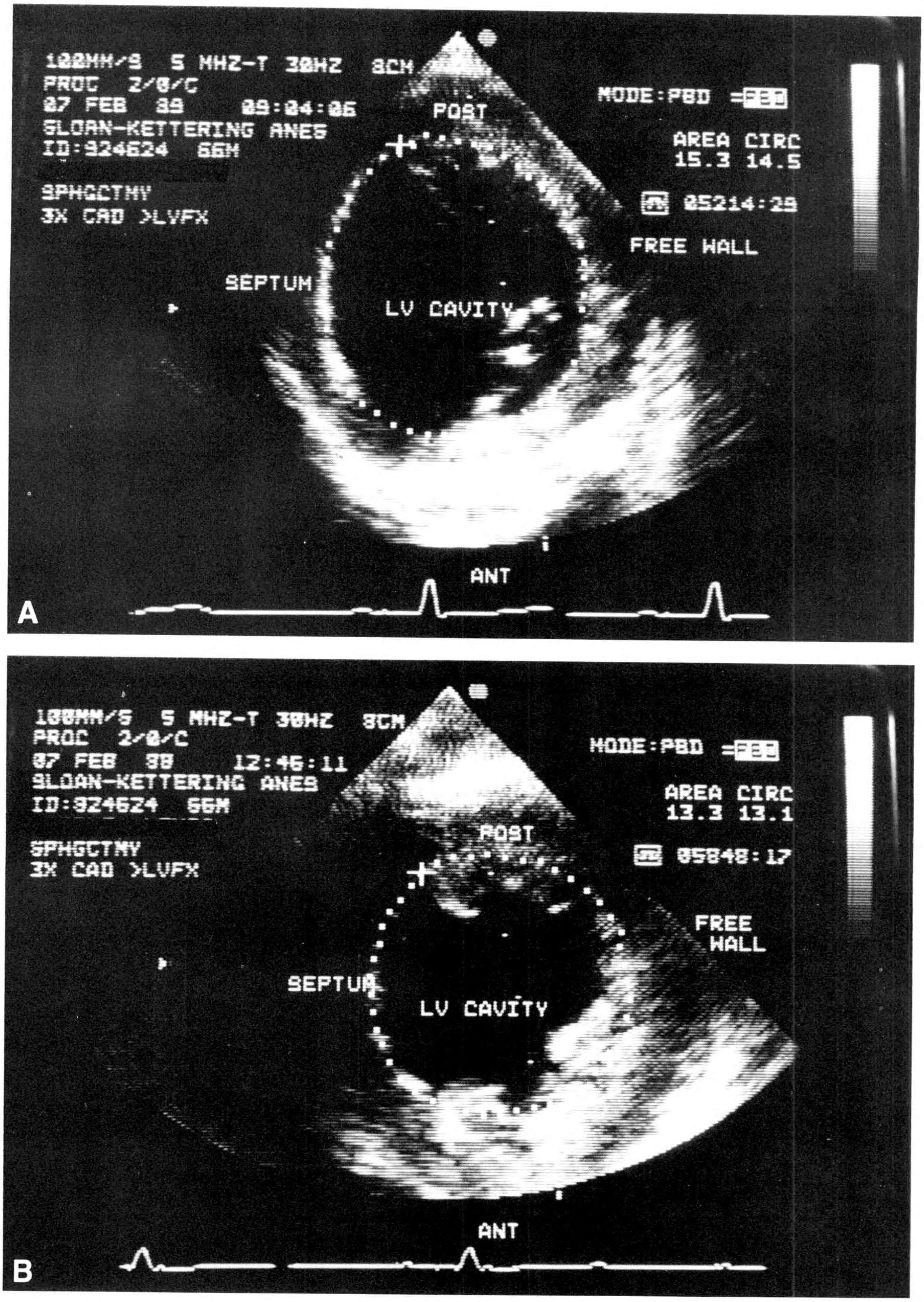

Figure 4. Short axis views obtained at midventricular level **(A)** before and **(B)** after the administration of enalaprilat. The LV is displayed to the right of the RV. Both views are obtained at end systole. Circumference and cross-sectional areas are marked.

diac output by both thermodilution and echocardiographic measurements. Preload and afterload reduction are known to reduce the ischemia resulting from high loading conditions. Thus, it appears that ACE inhibitors are particularly beneficial in cases of significant valvular insufficiency where afterload reduction may be beneficial, but where reflex tachycardia due to other afterload reducing agents could be detrimental (7). Although short-acting β-adrenoreceptor blockers could be used in similar clinical situations, their role is limited when ejection fraction is significantly impaired.

In summary, this case demonstrates the efficacy of the new ACE inhibitor, enalaprilat, in the rapid treatment of intraoperative left ventricular failure as graphically documented by 2D-TEE. In addition, we have shown the use of 2D-TEE to rapidly differentiate acute left ventricular failure from new-onset ischemia in patients with coronary artery disease.

References

1. Semple PF, Cumming AMM, Meredith PA, Morton JJ. Onset c action of captopril enalapril, enalaprilic acid and lisinopril i normal man. Cardiovasc Drugs Ther 1987;1:45–50.
2. Walinsky P, LeJemtel T, Powers ER, et al. Hemodynami benefits of single and multiple doses of intravenous enalaprila an angiotensin-converting-enzyme inhibitor. Heart Failur 1987;3:108–13.
3. Maskin CS, Ocken S, Chadwick B, LeMemtel TH. Comparativ systemic and renal effects of dopamine and angiotensin converting enzyme inhibition with enalaprilat in patients wit heart failure. Circulation 1985;4:846–52.
4. Kubo SH, Cody RJ, Laragh JH, et al. Immediate converting enzyme inhibition with intravenous enalapril in chronic congestive heart failure. Am J Cardiol 1985;55:122–6.
5. Chatterjee K, Parmley WW. Vasodilator therapy for acut myocardial infarction and chronic congestive heart failure. J A Coll Cardiol 1983;1:133–5.
6. Chatterjee K, Opie L. Angiotensin inhibitors and other vasod lators with special reference to congestive heart failure. Cardio vasc Drugs Ther 1987;1:1–8.
7. Amsterdam EA. Angiotensin-converting enzyme inhibition f congestive heart failure: achievements and potential. J Am Co Cardiol 1989;1:143–4.

Marked Sensitivity to Pancuronium in a Patient Without Clinical Manifestations of Myasthenia Gravis

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Key Words: COMPLICATIONS—myasthenia gravis. NEUROMUSCULAR RELAXANTS—pancuronium.

It is well known that anesthesia and surgery may precipitate muscle weakness in patients with myasthenia gravis (1), with some patients not recognized as myasthenics until such episodes (2,3). In such instances, the diagnosis of myasthenia gravis is usually based not only on the increased sensitivity to neuromuscular relaxants but also on the development of generalized muscle weakness after surgery, suggestive of exacerbation of mild or restricted type of myasthenia gravis by surgical stress. In this case report, we describe a patient with an increased sensitivity to pancuronium who, in spite of a high titer of antiacetylcholine receptor antibodies, showed no clinical manifestations of myasthenia gravis during the perioperative period.

Case History

A 74-yr-old woman, 37 kg in weight and 141 cm in height, was scheduled for gastrectomy for a gastric ulcer. She had no remarkable past medical history and was taking no medication. Physical examination was unremarkable and no signs of muscle weakness were observed. Preoperative laboratory findings were within the normal range.

The patient was premedicated with 0.4 mg of atropine IM. Immediately before induction of anesthesia, 1 mg of pancuronium was given intravenously to prevent succinylcholine-induced fasciculations. Two minutes after the administration of pancuronium, she became apneic and unresponsive. Ventilation with 100% oxygen was initiated. When pronounced fade on tetanic stimulation (50 Hz) by peripheral nerve stimulator was found, anesthesia was induced with 1.5% halothane and the trachea was intubated. Anesthesia was maintained with nitrous oxide (67%) and halothane (0.4%–1.5%) in oxygen. The patient required no additional doses of muscle relaxants during the 150 min of surgery. Although she was awake, responsive, and breathing spontaneously at the end of the operation, there was slight fade on tetanic stimulation. After administration of 1 mg of neostigmine with 0.5 mg of atropine, response to tetanic stimulation was sustained and her trachea was extubated. The postoperative course was uneventful and she showed no signs of muscle weakness.

Postoperatively, neurological examination was normal. There was no evidence of diplopia, ptosis, muscle weakness, or easy fatigability. Clinical tests of fatigability were negative. No abnormality in the neuromuscular transmission was demonstrated by single-fiber electromyography, a most sensitive and specific test for evaluation of normal neuromuscular transmission (4). A specific immunoprecipitation assay (5) revealed a very high titer of antiacetylcholine receptor antibodies (30.4 pmol/mL; normal range, <0.2 pmol/mL). Computed tomography demonstrated the presence of a thymoma in her anterior mediastinum.

Seven months after the gastrectomy, the patient was scheduled for total thymectomy. Before surgery, the patient gave written informed consent to participate in data collection protocols approved by the Ethical Committee of our institution. The patient was premedicated with 0.5 mg of atropine IM. After insertion of an IV catheter, she was given 100 μg of fentanyl and 5 mg of droperidol. After topical laryngotracheal anesthesia with 2 mL of 4% lidocaine, her

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Table 1. Effects of Incremental Doses of Pancuronium on Neuromuscular Transmission

	Time (min)[a]			
	0	10	20	30
Injection dose of pancuronium (mg)	0	0.1	0.2	0.6
Cumulative dose of pancuronium (mg)	0	0.1	0.3	0.9
Twitch height[b] (%)	100	100	74	2
Train-of-four ratio	1.0	1.0	0.71	T_1

T_1, only the first response to train-of-four stimulation was recorded.

[a] Effects of pancuronium were assessed 10 min after each injection. Baseline values were measured just before the injection of 0.1 mg of pancuronium. Each assessment except the last one was immediately followed by the next injection.

[b] Twitch height expressed as a percentage of baseline value.

trachea was intubated and anesthesia was started with 100 mg of thiamylal and maintained with 67% nitrous oxide in oxygen. Ten minutes after induction, the effect of pancuronium was examined in a dose-related manner using a neuromuscular transmission monitor (6). Injections of 0.1, 0.2 (total 0.3), and 0.6 (total 0.9) mg of pancuronium were made every 10 min and effects were assessed by measurement of twitch height and train-of-four ratio before each injection and 10 min after the last injection (0.6 mg) of pancuronium. The results are summarized in Table 1. The small doses of pancuronium blocked neuromuscular transmission in a dose-dependent manner. As muscle relaxation was sufficient after a cumulative dose of 0.9 mg of pancuronium, operation was started after administration of halothane. The operation was concluded with no additional doses of muscle relaxants. Reversal of neuromuscular blockade was achieved with 1.85 mg of neostigmine and 0.74 mg of atropine. The trachea was then extubated and the postoperative course was uneventful.

Discussion

It is a well-recognized fact that unexpected paralysis from a small dose of nondepolarizing muscle relaxants can be encountered in patients with undiagnosed myasthenia gravis (2,3). These patients represent a rare but important problem for anesthesiologists because such patients are usually not recognized as myasthenic until the development of prolonged postoperative apnea. In such cases, development of clinical myasthenia gravis after the operation as well as the increased sensitivity to neuromuscular relaxants often leads to the diagnosis of myasthenia gravis. Our patient also exhibited profound muscle weakness after a small, normally subparalyzing dose of pancuronium. The very high titer of antiacetylcholine receptor antibodies was suggested as a causative factor in her increased sensitivity to pancuronium. During induction of her second anesthesia for total thymectomy, the decreased margin of safety in neuromuscular transmission was demonstrated by measurement of twitch responses after the administration of pancuronium in small, incremental doses.

Unlike previously reported patients in whom myasthenia gravis was first identified during anesthesia and surgery (2,3), our patient had no clinical manifestations of myasthenia before, during, or after her first operation. Like Rogoff et al. (7) in their case, we did not make a diagnosis of clinical myasthenia gravis in our patient. It appeared that the decrease in the margin of safety in this patient was not severe enough to cause the failure of neuromuscular transmission in the usual, nonstressed state. This was supported by the fact that the amount of pancuronium required to produce a significant neuromuscular blockade in our patient was substantially greater than that needed to produce similar degrees of blockade in true cases of clinical myasthenia gravis as reported by Blitt et al. (8). Indeed, Cuenoud et al. (9) found high titers of antiacetylcholine receptor antibodies in 3 of 11 patients with a thymoma removed by operation but without clinical myasthenia gravis. They described these three patients as "premyasthenic state" and suspected that antibody titers or affinity to acetylcholine receptors might fall just short of being sufficient to induce myasthenic symptoms. Our patient appeared to be in the premyasthenic state, i.e., neuromuscular transmission was impaired in her even though she had no myasthenic symptoms.

The administration of a subparalytic dose of pancuronium before the administration of succinylcholine is a fairly common practice among anesthesiologists to avoid some of the undesirable side effects of succinylcholine. Small, priming doses of pancuronium have also been advocated to facilitate rapid tracheal intubation without using succinylcholine (10). As suggested by Schwarz et al. (11), our present case demonstrated an added advantage of small priming doses: prevention of serious perioperative complications resulting from unexpected sensitivity to nondepolarizing muscle relaxants in an apparently nonmyasthenic patient.

In summary, we report a case of increased sensitivity to pancuronium in a patient with no clinical manifestations of neuromuscular disorders. Although neurological examination was negative, a very high titer of antiacetylcholine receptor antibody and highly abnormal responses to the injection of small, incremental doses of pancuronium indicated the presence of a premyasthenic state.

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References

1. Gibbs PS, Kim KC. Skin and musculoskeletal diseases. In: Stoelting RK, Dierdorf SF, eds. Anesthesia and co-existing disease. New York: Churchill Livingstone, 1983:573–604.
2. Maharry JM, Sack RA. Prolonged postoperative apnea complicating gynecologic surgery: atypical cholinesterase and myasthenia gravis. Am J Obstet Gynecol 1984;143:36–40.
3. Wojciechowski APJ, Hanning CD, Pohl JEF. Postoperative apnea and latent myasthenia gravis: value of acetylcholine receptor antibody estimation in the differential diagnosis. Anaesthesia 1985;40:882–4.
4. Seybold ME. Myasthenia gravis. A clinical and basic science review. JAMA 1983;250:2516–21.
5. Ohta M, Matsubara F, Hayashi K, Nakao K, Nishitani H. Acetylcholine receptor antibodies in infants of mothers with myasthenia gravis. Neurology 1981;31:1019–22.
6. Viby-Mogensen J, Jensen E, Werner M, Kirkegaard Nielsen H. Measurement of acceleration: a new method of monitoring neuromuscular function. Acta Anaesthesiol Scand 1988;32:45–8.
7. Rogoff RC, Lippmann M, Walts LF. An unusual sensitivity to *d*-tubocurarine. Anesthesiology 1974;41:397–8.
8. Blitt CD, Wright WA, Peat J. Pancuronium and the patient with myasthenia gravis. Anesthesiology 1975;42:624–6.
9. Cuenoud S, Feltkamp TEW, Fulpius BW, Oosterhuis HJGH. Antibodies to acetylcholine receptor in patients with thymoma but without myasthenia gravis. Neurology 1980;30:201–3.
10. Mehta MP, Choi WW, Gergis SD, Sokoll MD, Adolphson AJ. Facilitation of rapid endotracheal intubation with divided dose of nondepolarizing neuromuscular blocking drugs. Anesthesiology 1985;62:392–5.
11. Schwarz S, Ilias W, Lackner F, Mayrhofer O, Foldes FF. Rapid tracheal intubation with vecuronium: the priming principle. Anesthesiology 1985;62:388–91.

Inorganic Fluoride and Prolonged Isoflurane Anesthesia in the Intensive Care Unit

Robert D. Truog, MD and Susan A. Rice, PhD

Key Words: ANESTHETICS, VOLATILE—isoflurane.

Isoflurane is a safe anesthetic for routine as well as for prolonged surgical procedures. It has also been employed in the intensive care unit (ICU) to treat conditions such as refractory status asthmaticus (1) or status epilepticus (2). These situations may require the administration of isoflurane for extended periods of time, well beyond the limits of documented safety. We report a case of prolonged isoflurane administration resulting in potentially nephrotoxic serum concentrations of inorganic fluoride (F^-).

Case Report

A 2-yr-old girl was admitted for correction of complex congenital heart lesions with cyanosis. Aside from her cardiac condition she had been healthy before surgery. The operative course was uneventful, but after surgery she developed continuous severe chorea. The presumed etiology was a lesion in the basal ganglia related to cardiopulmonary bypass. The chorea was only mildly responsive to multiple neuroleptic and sedative drugs, and her incessant writhing produced severe bleeding excoriations over her entire body.

Three weeks after surgery her physicians requested general inhalational anesthesia for several days in an attempt to suppress her movement, allow her skin to heal, and perhaps effect a remission. At the time medications included phenobarbital, phenytoin, reserpine, furosemide, aldactone, and oxacillin. After parental consent, general anesthesia was induced with midazolam, muscle relaxation was achieved with succinylcholine, and the trachea wa intubated. Anesthesia was maintained with isofl rane in 40% oxygen (O_2) and ventilation was cor trolled. Arterial blood gas tensions during the anes thetic were as follows: $P\text{CO}_2 = 37 \pm 3.8$, $P\text{O}_2 = 116$ 16.2, pH = 7.46 ± 0.05 (mean ± SD, $n = 23$). Th isoflurane concentration was titrated to stop he movements. Although she initially responded to a inspiratory concentration of only 0.6%, by the fift day she required 2.0%.

Inhalational anesthesia was discontinued afte 112 h. She had ~107 minimal alveolar concentratior hours (MAC-h) of isoflurane (MAC = 1.15%). Serur F^- concentrations were measured by an ion-specifi electrode after microdiffusion (National Medical Serv ices, Willow Grove, Pa.). The peak serum F^- concer tration was 36.8 μM after 73 MAC-h (Figure 1), th last sample obtained during the administration c isoflurane. There was a significant relationship be tween time of exposure to isoflurane and serum F concentration ($r = 0.91$, $P < 0.02$) (3). Four hours afte the isoflurane was discontinued the level had de creased to 17.4 μM.

There was no apparent change in renal functio during the anesthetic as evidenced by daily urinaly ses and serum blood urea nitrogen (BUN) and creat

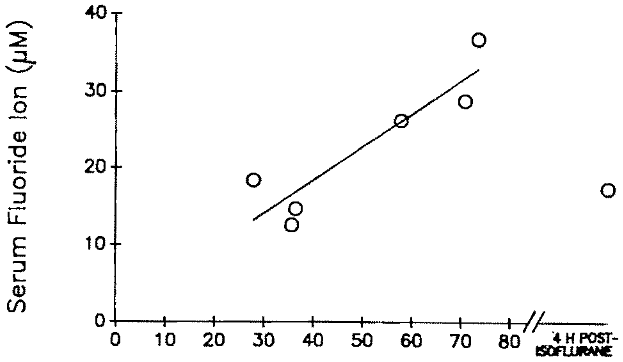

Figure 1. Serum fluoride levels vs MAC-hours of isoflurane. Th total anesthetic exposure was 107 MAC-h. The final level wa drawn 4 h after the anesthetic was discontinued ($r = 0.91$, $P < 0.0$ (3).

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Table 1. Renal, Hepatic, and Hematologic Indices During Prolonged Isoflurane Anesthesia

Index	8 h before isoflurane	MAC-h isoflurane 8.3	22.6	42.4	68.1	107.0	24 h after isoflurane
Serum creatinine (mg/dL)	0.4	0.4	0.4	0.2	0.2	0.4	0.2
BUN (mg/dL)	7	3	2	2	6	11	9
Urinary specific gravity	1.010	1.010	1.015	1.012	1.032	1.006	1.020
SGOT (mU/mL)	34	26	24		16	15	69
SGPT (mU/mL)	54	45	41	37	30	27	41
Lactate dehydrogenase (mU/mL)	333	253	239		173	201	265
Alkaline phosphatase (mU/mL)	71	72	71	62	52	59	57
Hemoglobin (g/dL)	13.1	12.3	11.0	11.1	10.9	9.1	8.9
White blood cell count (× 10^3/mL)	16.2	12.5	13.6	15.2	21.4	21 8	20.2
Platelet count (× 10^3/mL)	352			247	168	340	
Creatine phosphokinase (mU/mL)					11	11	996

inine concentrations (Table 1). After 68.1 MAC-h of isoflurane, urinary specific gravity was 1.032 with a normal urinalysis, implying no impairment in renal concentrating ability. There were also no significant changes in hepatic function as measured by serum levels of serum glutamic oxaloacetic acid transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactate dehydrogenase, and alkaline phosphatase. Her white blood cell count and platelet count remained stable, but her hemoglobin concentration decreased steadily, probably the result of multiple diagnostic phlebotomies. Her serum creatine phosphokinase and SGOT levels abruptly increased after the isoflurane was discontinued, most likely related to the sudden increase in her choreoathetoid movements. She remained hemodynamically stable throughout the anesthetic. She was extubated within 2 h of discontinuing the isoflurane, but unfortunately her movement disorder returned without any noticeable improvement.

Discussion

We report a patient treated with 107 MAC-h of isoflurane anesthesia. The peak measured serum F^- concentration of 36.8 μM is, to our knowledge, the highest serum F^- concentration documented with this agent in humans. Experience with methoxyflurane and enflurane anesthesia indicates that F^--induced nephrotoxicity initially manifests as an inability to concentrate urine and is generally associated with peak serum F^- concentrations >50 μM. Peak serum F^- concentrations as low as 33.6 μM may be nephrotoxic, however, when present for a prolonged period of time (4). The F^- concentrations attained in this patient suggest that prolonged administration of isoflurane may result in serum F^- concentrations that have been associated with nephrotoxicity under these conditions.

Several studies have investigated prolonged use of isoflurane. Revell et al. (5) described a child who had 73 MAC-h of isoflurane for status asthmaticus. The serum F^- levels peaked at 9.5 μM and there was no evidence of renal toxicity. Another case report documented a patient with status epilepticus who received ~68 MAC-h of isoflurane (2). Although serum F^- concentrations were not measured, urinary F^- elimination was not elevated, renal concentrating ability was maintained, and BUN and creatinine levels did not increase. Two additional case reports describe isoflurane anesthetics of 43- and 25-MAC-h duration but fail to comment on specific indices of renal toxicity or serum F^- concentrations (1,6). Oikkonen (7) studied seven patients given up to 6.7 MAC-h of isoflurane anesthesia. No renal effects were seen and the highest recorded serum fluoride concentration was 5.6 μM. Finally, in addition to the case presented, we administered 52 MAC-h of isoflurane to a 19-yr-old woman who developed a measured peak serum F^- concentration of 10.5 μM (unpublished data).

In addition to duration of exposure, metabolism of halogenated anesthetics is increased by drugs that enhance the activity of hepatic mixed-function oxidase systems. Treatment of rats with phenobarbital or phenytoin increases the in vitro release of F^- as a result of the metabolism of isoflurane (8). Both of these drugs probably contributed to the high serum F^- concentrations seen in our patient.

The patient whom we describe required an increasing inspiratory concentration of isoflurane to control her movements. Tolerance to isoflurane has not been reported in humans, and one study of mice chronically exposed to low concentrations of isoflurane for up to 63 days found no evidence of tolerance to this agent (9).

This case report shows that extended use of isoflurane in the ICU may result in serum F^- concentrations approaching nephrotoxic levels. The questionable safety of prolonged administration may become of greater concern if the use of isoflurane in ICUs becomes more prevalent. A recent letter describes the routine use of 0.5%–1.0% isoflurane for up to 150 h to sedate patients postoperatively (10). Although narcotics and benzodiazepines are currently the most commonly used sedatives in critical care medicine, isoflurane has properties that may make it an attractive alternative to these agents. Further studies must be done, however, to document its safety in this setting.

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References

1. Bierman MI, Brown M, Muren O, Keenan RL, Glauser F Prolonged isoflurane anesthesia in status asthmaticus. C Care Med 1986;14:832–3.
2. Kofke WA, Snider MT, Young RSK, Ramer JC. Prolonged lo flow isoflurane anesthesia for status epilepticus. Anesthesi ogy 1985;62:653–6.
3. Snedecor GW, Cochran WG. Statistical methods. Ames, Iow Iowa State University Press, 1980:184–5.
4. Mazze RI, Calverley RK, Smith NT. Inorganic fluoride nep rotoxicity: prolonged enflurane and halothane anesthesia volunteers. Anesthesiology 1977;46:265–71.
5. Revell S, Greenhalgh D, Absalom SR, Soni N. Isoflurane in t treatment of asthma. Anaesthesia 1988;43:477–9.
6. Pearson J. Prolonged anesthesia with isoflurane. Anesth Ana 1985;64:92–3.
7. Oikkonen M. Isoflurane and enflurane in long anaesthesias f plastic microsurgery. Acta Anaesthesiol Scand 1984;28:412–
8. Caughey GH, Rice SA, Kosek JC, Mazze RI. Effect of phen toin (DPH) treatment on methoxyflurane metabolism in ra J Pharmacol Exp Ther 1979;210:180–5.
9. Smith RA, Winter PM, Smith M, Eger EI. Tolerance to a dependence on inhalational anesthetics. Anesthesiology 197 50:505–9.
10. Beechey AP, Hull JM, McLellan I, Atherley DW. Sedation wi isoflurane (lett). Anaesthesia 1988;43:419–20.

846 ANESTH ANALG
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Isolated Postoperative Myoglobinuria in a Pediatric Outpatient

A Case Report of Malignant Hyperthermia

Patrick K. Birmingham, MD, George W. Stevenson, MD, Tetsu Uejima, MD, and
Steven C. Hall, MD

Key Words: HYPERTHERMIA, MALIGNANT. ANESTHESIA, PEDIATRIC. ANESTHESIA, OUTPATIENT.

Malignant hyperthermia (MH) may manifest itself by a variety of intraoperative signs. Unfortunately, its presentation may also be insidious, making diagnosis difficult.

We report a case of biopsy-proven MH in a pediatric outpatient in whom the presenting symptom was isolated postoperative myoglobinuria, incidentally noted just before hospital discharge.

Case Report

An 8-yr-old boy with an 8-mo history of dysphagia was scheduled for elective outpatient esophagogastroscopy. An esophagram and barium-cookie swallow 3 wk before esophagogastroscopy were normal. No other associated complaints were elicited from the patient or his parents.

Surgical history included a tonsillectomy performed at another institution 4 mo before admission. Anesthesia records of the case were not available, but the parents were unaware of any anesthetic or surgical complications. There was no family history of malignant hyperthermia or anesthesia-related problems.

Physical examination revealed a healthy-appearing, 29.7-kg boy in no distress, with an oral temperature of 37.1°C and a heart rate of 108 beats/min. Examination of the airway, heart, and lungs was unremarkable. Preoperative laboratory studies revealed a hemoglobin of 12.0 g/dL and a normal urinalysis.

After intramuscular premedication with 0.6 mg of atropine and 2.0 mg of midazolam, a precordial stethoscope, pulse oximeter, blood pressure cuff, and electrocardiogram (ECG) electrodes were placed, and anesthesia was induced with nitrous oxide (N_2O) and halothane in oxygen (O_2). The initial axillary temperature reading was 36.5°C. After preoxygenation, a single 60-mg IV dose (2 mg/kg) of succinylcholine was given to facilitate intubation with a cuffed 5.5-mm internal diameter oral RAE tracheal tube. No masseter muscle rigidity was noted with intubation.

Anesthesia was maintained with N_2O/O_2/halothane and proceeded uneventfully. No arrhythmias, arterial desaturation, tachypnea, muscle rigidity, or temperature elevation were noted. The heart rate was 140 beats/min upon arrival in the operating room and ranged from 140 to 150 beats/min during the procedure. End-tidal carbon dioxide was not monitored.

Esophagogastroscopy and pharyngoscopy revealed a small hypopharyngeal (Zenker's) diverticulum and a prominent cricopharyngeus muscle. After extubation when awake, the patient was taken to the recovery room, given supplemental oxygen by face mask, and monitored by ECG. Vital signs on arrival in the recovery room included an axillary temperature of 36.0°C, a respiratory rate of 32 breaths/min, and a pulse of 152 beats/min. The patient was transferred to the adjacent outpatient area 30 min later. Two hours later and almost 3.5 h after induction of anesthesia, he voided dark-colored urine, which was incidentally noted by the nursing staff.

The anesthesia service was notified and upon arrival found the patient to be awake, acyanotic, in no distress, taking fluids, watching television, and conversing with his parents. On questioning, he complained only of a mild sore throat. Vital signs at this

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time were a heart rate of 110 beats/min, a respiratory rate of 20 breaths/min, and an oral temperature of 37.5°C. Blood drawn had a creatinine phosphokinase (CPK) level of 19,635 IU/L (normal 35–232). Serum electrolyte levels included potassium at 4.4 mEq/L (normal 3.5–5.3) and CO_2 at 27.2 mEq/L (normal 23–30). A urine sample was positive for myoglobin. Arterial blood gas analysis was not done.

The patient's temperature ranged from 37.5° to 38.0°C orally over the next several hours. The heart rate ranged from 90 to 110 beats/min and the respiratory rate from 20 to 24 breaths/min. The patient remained awake, acyanotic, comfortable, and wished to go home. He was admitted to the hospital, however, for hydration, observation, and continuous monitoring. Because of concern that this might be early, albeit atypical, onset of MH, 2.5 mg/kg of dantrolene was given intravenously. The patient was discharged the following day after an uneventful night.

Eight months later, a vastus lateralis muscle biopsy was obtained under a nontriggering general anesthetic and, in a laboratory conforming to the guidelines of the Malignant Hyperthermia Association of the United States, tested positive for MH with exposure to 3% halothane, to caffeine alone, and to caffeine in the presence of 1% halothane. The patient's sister was subsequently tested and also found to be positive for MH. Testing of additional family members is pending.

Discussion

Myoglobinuria, although part of the clinical spectrum of MH, is an unusual presenting feature of the disorder. In the absence of additional evidence of MH or susceptibility to MH, myoglobinuria could easily be attributed to other factors, most notably the administration of succinylcholine. Visible myoglobinuria after the use of succinylcholine is well documented (1–12), with a reported incidence in children of 1 in 250 by one author (13).

The clinical presentation of malignant hyperthermia can be highly variable (14), however, and may present initially in the postoperative period. Any patient receiving general anesthesia is potentially at risk for MH; the ambulatory surgical patient is no exception. Although a "relative absence" of reported cases of MH in the ambulatory setting through 1982 has been noted by one author, the same author then identified six cases, three confirmed and three suspected, in 1983–1984 from approximately 50 reporting centers (15).

In our institution, the elective use of succinylcholine to facilitate tracheal intubation, especially after a halothane induction, has become less popular, as awareness of potential complications has increased. The likelihood of myoglobinemia (16,17), myoglobinuria (1,16,18), and MH (19) is increased when succinylcholine and halothane are used in combination. Additionally, myoglobinuria has been associated with acute postoperative renal failure (2,10–12,17), another factor to consider when using the combination of succinylcholine and halothane.

A serum CPK level of 20,000 IU/L after an episode of masseter spasm is believed to establish the diagnosis of MH in the absence of a muscle biopsy (20). No similar recommendation exists regarding myoglobinuria and an associated CPK elevation. If muscle biopsy testing were not available or the family refused testing, we would use nontriggering agents for any subsequent surgery.

In this case MH was suspected only after the patient was incidentally noted to void tea-colored urine. This raises the issue of whether ability to void and visual inspection of the urine should be a prerequisite to discharge from the pediatric ambulatory surgical unit, as well as after adult ambulatory surgery.

Voiding before discharge is commonly required in adults because of a higher incidence of postoperative urinary retention. A review of discharge criteria and anesthetic complications after pediatric outpatient surgery (21–30) reveals that few, if any, centers require infants and children to void before discharge, and that postoperative urinary retention in these younger patients, unlike adults, is exceedingly rare. A review of outpatient surgery looking specifically at pediatric urology patients (31) mentions no case of postoperative or postdischarge urinary retention and did not require patients to void before discharge. A single study (32) did mention a 7.6% incidence of "mild difficulty" in voiding after pediatric surgery, "mild" being defined as a complication "for which no action or intervention was required." A 1.1% incidence of "moderate difficulty" in voiding was also reported in this study, "moderate" meaning the "complication was one severe enough to call for some action . . . but not requiring the presence of a physician or hospitalization."

Our practice mirrors that of most other institutions in that the ability to void has not been, and is not currently, a criterion for discharge from the outpatient surgery unit. Nor have we seen a single case of urinary retention after discharge of day surgery patients with a normal genitourinary system (C. Firlit, personal communication).

Although we are not advocating institution of a policy requiring pediatric patients to void before discharge, we do recommend that any patient who voids tea-colored urine be further evaluated. Parents should be told to call the anesthesia department or on-call anesthesia personnel should they notice discoloration of the urine after discharge, assuming there is no other known cause for the discoloration (e.g., concurrent drug administration, ingestion of certain foods).

A second case at our institution has highlighted the importance of this recommendation. A healthy 4-yr-old girl, ASA physical status I, received a halothane/N_2O/O_2 general anesthetic for extensive dental restorations. Succinylcholine was used to facilitate intubation. The intraoperative and recovery room course was unremarkable. "Smokey" urine was incidentally noted before discharge from the outpatient area. Urinalysis was positive for myoglobin. The initial CPK was 47,852 IU/L and peaked the following morning at 69,495 IU/L. The patient was otherwise asymptomatic. There was no family history of muscle diseases or difficulty with surgery or anesthesia. She was given dantrolene, admitted for observation, and discharged 2 days later without sequelae. Renal function, as judged by urinalyses and serial measurement of serum blood urea nitrogen and creatinine levels, was normal. Muscle biopsy was recommended but to date has been refused by the family.

These cases emphasize the importance of a high index of suspicion for MH, even if the presenting symptoms or signs are atypical or seemingly minor. Although myoglobinuria may have other causes, at least one MH expert recommends diagnostic muscle biopsy for all patients who have myoglobinuria after anesthesia (33). We hope that additional clinical experience and follow-up will provide us with more definitive guidelines.

References

1. Airaksinen MM, Tammisto T. Myoglobinuria after intermittent administration of succinylcholine during halothane anesthesia. Clin Pharmacol Ther 1966;7:583–7.
2. Bennike KA, Jarnum S. Myoglobinuria with acute renal failure possibly induced by suxamethonium. Br J Anaesth 1964;36:730–6.
3. Lewandowski KB. Strabismus as a possible sign of subclinical muscular dystrophy predisposing to rhabdomyolysis and myoglobinuria: a study of an affected family. Can Anaesth Soc J 1982;29:372–6.
4. Moore WE, Watson RL, Summary JJ. Massive myoglobinuria precipitated by halothane and succinylcholine in a member of a family with elevation of serum creatine phosphokinase. Anesth Analg 1976;55:680–2.
5. Jensen K, Bennike KA, Hanel HK, Olesen H. Myoglobinuria following anaesthesia including suxamethonium. Br J Anaesth 1968;40:329–34.
6. McLaren CAB. Myoglobinuria following the use of suxamethonium chloride. Br J Anaesth 1968;40:901–2.
7. Harrington JF, Ford DJ, Striker TW. Myoglobinemia and myoglobinuria after succinylcholine in children (abstr). Anesthesiology 1983;59:A439.
8. Tammisto T, Airaksinen MM. Suxamethonium-induced myoglobinuria. Br J Anaesth 1965;37:464.
9. Lewandowski KB. Rhabdomyolysis, myoglobinuria and hyperpyrexia caused by suxamethonium in a child with increased serum creatine kinase concentrations. Br J Anaesth 1981;53:981–4.
10. Pellicci PM, Paget S, Tsairis P. Post-anesthetic myoglobinuria with acute renal failure (normothermic malignant hyperthermia). J Bone Joint Surg (Am) 1983;65-A:413–4.
11. McKishnie JD, Muir JM, Girvan DP. Anaesthesia induced rhabdomyolysis—a case report. Can Anaesth Soc J 1983;30:295–8.
12. Hool GJ, Lawrence PJ, Sivaneswaran N. Acute rhabdomyolytic renal failure due to suxamethonium. Anaesth Intensive Care 1984;12:360–4.
13. Ploetz J. Succinylcholine in children. Anesth Analg 1988;67:801.
14. Braude BM, Press P, Moyes DG, Isaacs H, Danilewitz MD, Kolb ME. Unexpected hyperthermia manifesting during outpatient anesthesia. Anesthesiology 1986;64:647–50.
15. Natof HE. Complications. In: Wetchler BV, ed. Anesthesia for ambulatory surgery. Philadelphia: JB Lippincott, 1985:321–56.
16. Katz RL, Katz LK. Complications associated with the use of muscle relaxants. In: Orkin FK, Cooperman LH, eds. Complications in anesthesiology. Philadelphia: JB Lippincott, 1983:557–79.
17. Blanc VF, Vaillancourt G, Brisson G. Succinylcholine, fasciculations and myoglobinaemia. Can Anaesth Soc J 1986;33:178–84.
18. Tammisto T, Airaksinen M. Increase of creatine kinase activity in serum as sign of muscular injury caused by intermittently administered suxamethonium during halothane anaesthesia. Br J Anaesth 1966;38:510–5.
19. Ording H. Incidence of malignant hyperthermia in Denmark. Anesth Analg 1985;64:700–4.
20. Rosenberg H, Fletcher JE. Masseter muscle rigidity and malignant hyperthermia susceptibility. Anesth Analg 1986;65:161–4.
21. Johnson GC. Day care surgery for infants and children. Can Anaesth Soc J 1983;30:553–7.
22. Meridy HW. Criteria for selection of ambulatory surgical patients and guidelines for anesthetic management: a retrospective study of 1553 cases. Anesth Analg 1982;61:921–6.
23. Steward DJ. Experiences with an outpatient anesthesia service for children. Anesth Analg 1973;52:877–80.
24. Steward DJ. Outpatient pediatric anesthesia. Anesthesiology 1975;43:268–76.
25. Ahlgren EW, Bennett EJ, Stephen CR. Outpatient pediatric anesthesiology: a case series. Anesth Analg 1971;50:402–8.
26. Steward DJ. Anesthesia for day-care surgery: a symposium. Anaesthesia for paediatric out-patients. Can Anaesth Soc J 1980;27:412–6.
27. Patel RI, Hannallah RS. Anesthetic complications following pediatric ambulatory surgery: a 3-yr study. Anesthesiology 1988;69:1009–12.
28. Ahlgren EW. Pediatric outpatient anesthesia. A four-year review. Am J Dis Child 1973;126:36–40.

29. Natof HE. Complications associated with ambulatory surgery. JAMA 1980;244:1116–8.

30. Cloud DT, Reed WA, Ford JL, Linkner LM, Trump DS, Dorman GW. The surgicenter: a fresh concept in outpatient pediatric surgery. J Pediatr Surg 1972;7:206–12.

31. Kroowand RL, Perlmutter AD. Short stay surgery in pediatric urology. J Urol 1978;120:483–4.

32. Davenport HT, Shah CP, Robinson GC. Day surgery for children. Can Med Assoc J 1971;105:498–501.

33. Rosenberg H. Clinical presentation of malignant hyperthermia. Br J Anaesth 1988;60:268–73.

Letters to the Editor

Alfentanil Partition Coefficient

Key Words: ANALGESICS, ALFENTANIL.

To the Editor:

Dr. Jos Heykants has informed us that there was a typographic error in his original publication from which Dr. DiFazio and I calculated the octanol: water partition coefficient for alfentanil (1,2). This error caused us to report the partition coefficient as 14 rather than 140.

We would also like to correct the calculated brain lipid concentrations in Table 1, which should have been micromolar rather than millimolar (2).

In conclusion, the change in calculated alfentanil brain lipid concentration has a greater deviation from the other opiates considered in our paper. However, the change from millimolar to micromolar does not alter our conclusions.

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References

1. Meuldermans WEG, Hurkmans RMA, Heykants JJP. Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. Arch Int Pharmacodyn 1982;257:4–19.
2. Stone DJ, DiFazio CA. Anesthetic action of opiates: correlations of lipid solubility and spectral edge. Anesth Analg 1988;67:663–6.

The Beelzebub Nitrogen and Preoxygenation

Key Words: COMPLICATIONS, OBESITY. VENTILATION, PREOXYGENATION.

To the Editor:

Goldberg et al. compared two different techniques for preoxygenating morbidly obese patients (1). Their conclusion was that four vital capacity (VC) breaths of 100% oxygen (O_2) over 30 s may be more appropriate than 3 min of normal tidal breathing of 100% oxygen, as both techniques were associated with similar increases in Pao_2 (note the error in the original text on page 521, as the authors reported "similar increases in '$Paco_2$'"). This recommendation was based in part on their observation that the latter technique was associated with mild carbon dioxide (CO_2) retention.

Of concern to me was that despite the physical constitution of the patients studied (mean weight >137 kg) and their associated increased alveolar ventilation (2), the fresh gas inflow used in the study by Goldberg et al. (1) was only 4 L/min through a conventional circle system and face mask. Compensation for the increased O_2 consumption and CO_2 production in the morbidly obese is accomplished by increases in both cardiac output and alveolar ventilation (2). By my calculations, the group employing "4 VC breaths over 30 seconds" was at considerable risk of rebreathing significant amounts of exhaled nitrogen. In my estimation, the failure to measure end-tidal nitrogen represents a serious weakness in the study design and mitigates against its clinical application. An associated weakness in not measuring end-tidal or circuit nitrogen was the use of a "tight-fitting face mask," a technique that unless meticulously executed, can result in significant entrainment of room air (3). It is of interest that two recent studies examining this issue found that the use of four VC breaths was inconsistently effective in achieving appropriate alveolar oxygenation in pregnant parturients (4,5).

Preoxygenation of the morbidly obese patient (as well as any other patient to whom the technique is applied) is directed not only at increasing the Pao_2 but also, and perhaps of greater clinical moment, to washing out the functional residual capacity of nitrogen, replacing it with O_2, and providing a physiologic buffer and reservoir. Contemporary studies must attend to these related but separate components of preoxygenation techniques if they are to provide practitioners with sufficient information upon which to judge their clinical merit.

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References

1. Goldberg ME, Norris MC, Larijani GE, Marr AT, Seltzer JL. Preoxygenation in the morbidly obese: a comparison of two techniques. Anesth Analg 1989;68:520–2.

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2. Vaughan R. Pulmonary and cardiovascular derangements in the obese patient. In: Brown BR Jr, ed. Anesthesia and the obese patient. Philadelphia: FA Davis, 1982:19–39.
3. Drummond G, Park G. Arterial oxygen saturation before intubation: an assessment of oxygenation techniques. Br J Anaesth 1984;56:987–93.
4. Russell G, Smith C, Snowden S, Bryson T. Preoxygenation and the parturient patient. Anaesthesia 1987;42:346–51.
5. Sellers W, Rhodin A. Pre-oxygenation. Br J Anaesth 1985;57:1268–9.

In Response:

We appreciate Mr. Biddle's comments concerning our study (1). We agree with him on the question of fresh gas flow rate and nitrogen accumulation within the circle system. We have studied nitrogen washout in a group of nonobese subjects and noted accumulation of nitrogen within the circle anesthesia system when using either technique at 4-L/min gas flow. Increasing fresh gas flow to 8 L/min improves nitrogen washout when using the 3-min technique while increasing fresh gas flow to the maximum deliverable by the anesthesia machine (14–18 L/min) improves nitrogen washout with the four-deep-breath technique (unpublished results). Parturients with their smaller functional residual capacity's achieve adequate denitrogenation with either technique at 8-L/min fresh gas flow (2). While we have not studied denitrogenation in obese subjects, we would predict that they would behave as the parturients as they also have markedly diminished functional residual capacity (3).

Mr. Biddle is correct that monitoring a leak-free mask fit is essential for preoxygenation with the four-breath technique; however, it has long been known that mask leaks can also significantly hinder preoxygenation during tidal breathing (4).

Clinically, both preoxygenation techniques produce similar increases in Pa_{O_2} and provide adequate oxygenation during rapid sequence induration and intubation. While the 3-min technique may provide slightly better denitrogenation and protection against apnic hypoxemia (5), continuous monitoring of oxygen saturation allows the anesthesiologist to assess oxygenation throughout induction and intubation regardless of preoxygenation technique.

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References

1. Goldberg ME, Norris MC, Larijani GE, Marr AT, Seltzer JL. Preoxygenation in the morbidly obese: a comparison of two techniques. Anesth Analg 1989;68:520–2.
2. Norris MC, Kirkland MR, Torjman MC, Goldberg ME. Denitrogenation in pregnancy. Anesth Analg 1989;68:S213.
3. Hedenstierna G, McCarthy G. Mechanics of breathing, gas distribution and functional residual capacity at different frequencies of respiration during spontaneous and artificial ventilation. Br J Anaesth 1975;47:705–12.
4. Hamilton WK, Eastwood DW. A study of denitrogenation with some inhalation anesthetics systems. Anesthesiology 1955;16:862–7.
5. Gambee AM, Hertzka RE, Fisher DM. Pre-oxygenation techniques: comparison of three minutes and four breaths. Anesth Analg 1987;66:468–70.

Pulse Oximeters

Key Words: MEASUREMENT TECHNIQUES—oximetry. OXYGEN, MEASUREMENT—oximetry.

To the Editor:

In a recent paper (1) Alexander, Teller, and Gross reported on their findings in a comparison of pulse oximeters. The background information on the principles of pulse oximetry and the section on the limitations of the technique are useful to all practitioners currently employing the monitoring technique. A thorough understanding of how a piece of equipment works as well as what might cause it to perform in a way other than expected is helpful in obtaining the best possible results.

I would like to take exception to one significant deficiency in the comparison of the nine pulse oximeters. As mentioned, the pulse oximeters ranged in suggested price from $1800 to $6000. This wide range should immediately suggest to the reader that the authors in looking at the features of these oximeters were not comparing apples to apples. I propose that another column be added to the comparison, and cost be ranked as one of the criteria. Further, I would suggest that the results of the rankings would then be significantly different.

Whenever evaluating equipment or techniques, one needs to ask oneself what is the intended end result. If patient protection from hypoxemia is the desired end product, then accurate reliable Sa_{O_2} and pulse rate information is the criterion on which the evaluation should be based. And if the number of pieces of equipment that can be purchased is limited by a set budgetary figure, then the price of the product becomes another factor in the decision-making process. It is unfortunate that capital equipment budgets are often strained and many people and products are competing for limited dollars. We cannot ignore this important fact when evaluating equipment.

Additionally, while I welcome any comparison of our pulse oximeters to other manufacturers' products, I would hope that authors would take into consideration that the field of patient monitoring is rapidly changing. There will be major changes and enhancements in all products between the completion of any study and publication of the results. All results should be judged within this context.

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1. Alexander CM, Teller LE, Gross JB. Principles of pulse oximetry: theoretical and practical considerations. Anesth Analg 1989;68:368–76.

In Response:

Ms. Faubert raises valid concerns regarding the decision process for selecting pulse oximeters. Clearly, in this era of finite resources, cost is an important factor in all equipment purchasing decisions. However, we specifically excluded cost from our rankings table (1) for the following reasons:

1. Oximeters are often sold at considerable discounts from the list prices; some manufacturers have offered three-for-the-price-of-two incentives, while others offer large discounts for volume purchasers. Therefore, we felt it more appropriate for purchasers to determine their final cost for the oximeter(s) in which they are interested, rather than for us to tabulate the list prices published by the manufacturers.
2. Any attempt to include price in our overall rankings would have required that we somehow relate cost to oximeter performance. This relationship would be expected to vary between institutions depending upon the availability of funding; therefore, the general applicability of our findings would be decreased.

The Criticare 501+ oximeter, like several of the others we evaluated, lacks several features which we consider important in choosing a pulse oximeter. Specifically, the pulse-beep indication does not change in pitch with S_pO_2, its alarm sound is difficult to localize (it sounds like a paging beeper), and it does not perform well when placed on the same arm as a blood pressure cuff. Additionally, its large, outboard, power transformer covers two duplex outlets, and is likely to break if accidentally dropped on the floor. Based upon its overall performance, it appeared in the middle of our rankings.

Interestingly, Criticare makes a more advanced pulse oximeter, the model 502. Unfortunately, although it had been introduced before the beginning of our evaluation, the manufacturer did not choose to send this full-featured model for evaluation.

We recognize that the field of patient monitoring is rapidly changing; therefore, we believe that it is most important to understand the principles underlying our evaluations before reaching a decision. On this basis, it should be possible to compare newly introduced oximeters in an informed, rational manner.

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1. Alexander CM, Teller LE, Gross JB. Principles of pulse oximetry: theoretical and practical considerations. Anesth Analg 1989;68:368–76.

Lumbar Plexus Blocks and Lumbar Plexus Nerve Blocks

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—lumbar plexus block.

To the Editor:

We read with interest the report by Parkinson et al. (1) on lumbar plexus blocks and we congratulate the authors for this well-conducted study. However, we would like to make three comments.

Our first remark deals with anatomy. As stated in the paper, the fifth lumbar nerve may emerge below the psoas muscle but, in most cases, it does not: the psoas muscle usually "arises from 1) the anterior surface and lower borders of the transverse processes of all the lumbar vertebrae, 2) by five digitations, each from the bodies of two vertebrae and their intervertebral disc (. . .)" (2). Even when uncovered by the muscle at its emergence from the spinal canal, this nerve runs only a short distance within the paravertebral space before it enters the psoas fascia and muscle. Although we occasionally have contacted it while it traversed the paravertebral space, we believe it more likely that we reached its perineural space within the substance of the psoas muscle (3). Because (a) the epineurium of spinal nerves is in continuity with the dura mater, and (b) the epidural solution may spread a considerable distance along spinal nerves (4), the local anesthetic might have spread along the nerve in the direction of the epidural space without diffusing within the paravertebral space. Recently, one of our pediatric patients developed spinal anesthesia following Winnie's technique of lumbar plexus block (5). The spread of the local anesthetic toward the subarachnoid space could not be explained by the paravertebral hypothesis. The site of injection (and insertion route of the block needle) was such that neither direct penetration of the subarachnoid space nor puncture of an arachnoid granulation protruding through the spinal dura (a common event in the root sleeve region, close to the spinal ganglia) could have occurred. The more likely hypothesis is still that of direct spread from the perineural space, along the perineurium, in the direction of the spinal canal. We should keep in mind that the limits between the subarachnoid, epidural, and perineural spaces are variable, even in adults, and that unexpected (and usually undesirable) diffusion of local anesthetic along the neuraxis may occasionally occur after a technically well-performed peripheral nerve block.

Another point we would like to comment on is the assessment of the "3-in-1" block as a lumbar plexus block. The lumbar plexus lies entirely within the substance of the psoas muscle; only peripheral nerves issuing from the lumbar plexus, not the lumbar plexus itself, emerge from its borders. Furthermore, the only lumbar plexus nerves contacting the quadratus lumbarum muscle (and its aponeurosis) are the ilioinguinal, iliohypogastric, lateral femoral cutaneous, and genitofemoral nerves. In their original article, Winnie et al. (6) reported certain clinical data that must be considered basically sound, particularly as they were subsequently confirmed by clinical practice in a number of patients. In their hypotheses aimed at providing an explanation for these clinical features, they suggested that the anesthetic could spread medially in the direction of the lumbar plexus and, in support of this, they provided x-rays taken after injection of contrast material (6). However, none of the illustrations showed spread of the anesthetic solution medially enough to be consistent with this hypothesis. Even if the local anesthetic entered the space between the psoas and quadratus lumbarum muscles, only the four nerves emerging at this level would have been blocked: in reality, the 3-in-1 block would have become a 4-in-1 block (plus femoral nerve block), but with no effect upon the obturator nerve. This is, basically, what Parkinson et al. observed (1). In any case, 3-in-1 blocks should not be considered lumbar plexus blocks but only multieffective lumbar plexus nerve blocks.

The fact remains that a number of patients, and not only those from Winnie's study (6), have developed readily evident obturator nerve blockade after "3-in-1" blocking procedures. In addition, several cases of unexpected blockade of lumbar plexus nerves have been reported following various blocking procedures. Sharrock (7) and also Lonsdale (8) have observed inadvertent 3-in-1 blocks following attempts to block the lateral femoral cutaneous nerve only. Roy-Shapira et al. (9) reported two pediatric cases of transient quadriceps paresis following local inguinal block. It can be suspected that a link exists between these apparently unrelated events. This link may be the complex fascia covering both the iliacus and psoas muscles, from the lumbar paravertebral area to the upper part of the thigh, i.e., the fascia iliaca.

All the nerves issuing from the lumbar plexus run a significant part of their course immediately below the fascia iliaca at their emergence from the psoas muscle. Thus, if a sufficient volume of local anesthetic is injected below this fascia, it may contact all of the lumbar plexus nerves, including the obturator nerve. This may occur (a) when the block needle enters the sheath surrounding each lumbar plexus nerve, or (b) if the fascia iliaca, which lies below the fascia lata at the level of the thigh, is either involuntarily punctured during an attempt to block the lateral cutaneous nerve of the thigh or deliberately overpassed to achieve what we call a "fascia iliaca compartment block" (10,11). Because of the emergence of the obturator nerve at the lateral border of the psoas muscle, only large amounts of local anesthetics can reach the nerve, as observed by Winnie et al. (6).

The last point we would like to comment on is the methodology for evaluating nerve blockade. The lateral femoral cutaneous nerve is thin and divides into two still thinner terminal branches at the level of the inguinal ligament. Furthermore, it is a sensory nerve, i.e., it is formed by unmyelinated and poorly myelinated nerve fibers only. Such a nerve is extremely easy to block with small amounts of local anesthetic. Conversely, the femoral nerve is a large mixed nerve: thus one might expect that blocking its richly myelinated A-α motor fibers would require larger amounts of anesthetic. However, the femoral nerve divides in several terminal branches at the level of, or immediately below, the inguinal ligament. When sensory or motor blocks develop in dermatomes and myotomes supplied by the femoral nerve, they may result from blockade of either the main trunk or, more likely, its division branches (thinner, thus easier to block with low-concentration anesthetic solutions).

On the other hand, the obturator nerve is a large nerve that divides into two branches that are also large before entering the thigh. The latter divide into terminal branches at a distance from their emergence from the psoas border that is considerably greater than is seen with the femoral nerve. As it is mainly a motor nerve, the obturator nerve is formed by largely myelinated fibers that require higher concentrations of local anesthetics to be blocked. Even if small amounts of the local anesthetic injected by Parkinson et al. (1) had reached the obturator nerve (following 3-in-1 block), it can be imagined that most motor fibers might have remained unaffected, whereas sensory fibers could have been blocked (we agree that evaluating the sensory distribution of the obturator nerve is difficult). We believe that the methodology of Parkinson et al. does not permit the conclusion that the local anesthetic cannot reach the obturator nerve following 3-in-1 blocks. The problem of reliability and safety of obturator nerve block by the 3-in-1 approach or of multieffective sacral plexus nerve block by posterior lumbar plexus approaches is different. While we believe that such attempts can be successful, we agree with Parkinson et al. (1) that neither procedure (i.e., 3-in-1 block for blocking the obturator nerve and posterior lumbar plexus block for blocking sacral plexus nerves) is both reliable and safe because of the large doses of local anesthetic needed. Neither procedure should be recommended when such distant nerves are to be blocked.

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References

1. Parkinson SK, Mueller JB, Little WL, Bailey SL. Extent of blockade with various approaches to the lumbar plexus. Anesth Analg 1989;68:243–8.
2. Williams PL, Warwick R. The fasciae and muscles of the lower limb. In Williams PL, Warwick R, eds. Gray's anatomy. 36th ed. Philadelphia: WB Saunders, 1980:593.
3. Dalens B, Tanguy A, Vanneuville G. Lumbar plexus block in children: a comparison of two procedures in 50 patients. Anesth Analg 1988 67:750–8.
4. Dalens B, Haberer JP. Epidural anesthesia in children. Anesthesiology 1987;66:714–5.
5. Winnie AP, Ramamurthy S, Durrani Z, Radonjic R. Plexus block for lower extremity surgery. Anesthesiol Rev 1974;1:11–6.
6. Winnie AP, Ramamurthy S, Durrani Z. The inguinal paravascular technique of lumber plexus anesthesia: the "3-in-1" block. Anesth Analg 1973;52:989–96.

7. Sharrock NE. Inadvertent "3-in-1" block following injection of the lateral cutaneous nerve of the thigh. Anesth Analg 1980;59:887–8.
8. Londsdale M. 3-in-1 block: confirmation of Winnie's anatomical hypothesis. Anesth Analg 1988;67:601–2.
9. Roy-Shapira A, Amoury RA, Ashcraft KW, Holder TM, Sharp RJ. Transient quadriceps paresis following local inguinal block for postoperative pain control. J Pediatr Surg 1985;20:554–5.
10. Dalens B. Lower limb blocks. In: Dalens B, ed. Pediatric regional anesthesia. Boca Raton: CRC Press, 1989.
11. Dalens B, Vanneuville G, Tanguy A. Comparison of the fascia iliaca compartment block with the 3-in-1 block in children. Anesth Analg 1989;69:705–13.

In Response:

We appreciate the comments by Dalens et al. and feel that this provides an appropriate forum to discuss several issues regarding lower extremity anesthesia.

Perhaps our methodology does not permit the conclusion that the local anesthetic cannot reach the obturator nerve following 3-in-1 blocks (inguinal paravascular technique), but we continue to contend that it does not travel proximally far enough in sufficient quantity to block the obturator nerve, even at doses of 0.5 mL/kg. Dalens, in his paper on lumbar plexus block in children (1), stated that the obturator nerve may remain unaffected in a number of cases in which the 3-in-1 block is used. We perform 10–20 leg block anesthetics weekly at our institution and routinely use them as the sole anesthetic for major knee surgery (e.g., ligament reconstruction, total knee replacement). The 3-in-1 block (in combination with a sciatic nerve block), because it spares the obturator nerve, has routinely proven to be inadequate for significant knee surgery. Our combined experience approximates 2000 leg-block anesthetics, and we have yet to see a complete obturator nerve block after a 3-in-1 approach was used. This is not meant to imply that the inguinal paravascular approach is not useful, for it is an effective and simple block for many procedures requiring anesthesia or analgesia of the lower extremity in the distribution of the femoral and lateral femoral cutaneous nerves.

The original paper by Winnie et al. on the inguinal paravascular approach (2) introduced an excellent technique and is quoted frequently in many anesthesia textbooks. However, we seriously challenge the results with regard to the technique's efficacy for blocking the obturator nerve. It is in reality a functional 2-in-1 block (femoral and lateral femoral cutaneous nerves) (3). The original article did not state how the various nerves were assessed. If successful surgery was the determinant, then a list of the procedures performed and supplementation required should have been included. Perhaps an unbiased observer should attempt a study in which the 3-in-1 block, along with sciatic nerve block, is evaluated as the primary anesthetic for a series of patients undergoing total knee reconstruction or knee replacement. The problem lies in the paucity of institutions performing leg-block anesthetics on a regular basis, thus work in this area may go (and has gone) years without substantiation or repudiation.

The lumbosacral plexus block proposed in another oft-quoted paper (4) was neither studied nor evaluated by the authors in that particular treatise. Yet, the idea of combined lumbar and sacral plexus blockade (or its peripheral nerve equivalent) from a single posterior approach persists in a number of anesthesia texts, even though no studies document it. To date, no true ipsilateral lumbosacral plexus block, providing complete anesthesia of the lower extremity with a single injection, has been proven.

Greene addressed the problem of semantics and regional anesthesia in a recent editorial (5), focusing mainly on spinal and epidural terminology. Similar concern for the nomenclature of lower extremity anesthesia is appropriate. The terms "3-in-1 block" and "lumbosacral plexus block" are misleading and should be discarded or renamed (such as the 2-in-1 block and the psoas compartment block).

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References

1. Dalens B, Tanguy A, Vanneuville G. Lumbar plexus block in children: a comparison of two procedures in 50 patients. Anesth Analg 1988; 67:750–8.
2. Winnie AP, Ramamurthy S, Durrani Z. The inguinal paravascular technique of lumbar plexus anesthesia: the "3-in-1" block. Anesth Analg 1973;52:989–96.
3. Parkinson SK, Mueller JB, Little WL, Bailey SL. Extent of blockade with various approaches to the lumbar plexus. Anesth Analg 1989;68:243–8.
4. Winnie AP, Ramamurthy S, Durrani Z, Radonjic R. Plexus blocks for lower extremity surgery. Anesthesiol Rev 1974;1:11–6.
5. Greene NM. Another Tower of Babel? Reg Anesth 1989;14:2–3.

Coronary Artery Vasospasm Following Placement of a Cold Liver Graft During Orthotopic Liver Transplantation

Key Words: SURGERY, TRANSPLANTATION—liver. LIVER, TRANSPLANTATION—coronary spasm.

To the Editor:

We wish to report a complication of orthotopic liver transplantation (OLT) that has not been previously described.

A 19-yr-old white female patient with Wilson's disease developed fulminant liver failure and underwent OLT. Liver function progressively deteriorated over the next 6 mo as a result of chronic rejection. A second liver transplant was therefore planned. The preoperative evaluation demonstrated normal cardiovascular function.

The operation proceeded uneventfully until the anhepatic phase. Immediately after placement of the cold donor

Table 1. Benzyl Alcohol Content of Drugs Used in Anesthesia

Drug, concentration	Manufacturer	Vial volume (mL)	Amount of benzyl alcohol (mg/mL)
Succinylcholine, 20 mg/mL	Organon	10	10
Pancuronium, 1 mg/mL	Organon	10	10
Atracurium, 10 mg/mL	Burroughs-Welcome	10	9
d-Tubocurarine, 3 mg/mL	Squibb	10	9
Midazolam, 5 mg/mL	Roche	1	10
Diazepam, 10 mg/mL	Roche	1	10
Atropine, 0.4 mg/mL	Elkins-Sinn	20	15
Glycopyrrolate, 0.2 mg/mL	American Regent Lab	5	9
Heparin, 1000 U/mL	Elkins-Sinn	10	10
	Wyeth	10	10
	Upjohn	10	10
Doxapram, 1 mg/mL	AH Robbins	20	9
Aminocaproic acid, 250 mg/mL	Lederle	20	9
Procainamide, 500 mg/mL	ESI Pharmac	2	9

liver into the abdomen, the patient developed a nodal rhythm with inverted P waves and 0.9-mV ST segment elevation in lead II. Nifedipine (10 mg) was given sublingually. ST segment elevation decreased to 0.5 mV and sinus rhythm returned within 5 min. Pulmonary artery temperature decreased from 34.9° to 33.9°C on initiation of venovenous bypass. It further decreased to 33.4°C at the time of placement of the liver in the abdomen and to 32.5°C following graft reperfusion. By this time, ST segment elevation decreased to 0.2 mV and then gradually became isoelectric. The procedure concluded uneventfully.

Coronary vasospasm provoked by a cold pressor test has been reported (1,2), but not in the context of OLT. We believe that these events resulted from the placement of the cold liver immediately beneath the diaphragm, with conduction of the cold temperature to the lower surface of the heart causing vasospasm of the right coronary artery. This was partially relieved by nifedipine, but did not resolve completely until the liver graft was reperfused and thus rewarmed. Major hemodynamic changes may take place during graft reperfusion, and an ischemic heart may be less able to respond well to these events. Therefore, we recommend continuous ST segment monitoring during OLT.

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References

1. Kaski JC, Crea F, Meran D, et al. Local coronary supersensitivity to diverse vasoconstrictive stimuli in patients with variant angina. Circulation 1986;74:1255–65.
2. Shea DL, Ockene IS, Greene HL. Acute myocardial infarction provoked by a cold pressor test. Chest 1981;80:649–51.

Inadvertent Benzyl Alcohol Administration in Neonates: Do We Contribute?

Key Words: TOXICITY, BENZYL ALCOHOL. ANESTHESIA, PEDIATRIC—benzyl alcohol toxicity.

To the Editor:

Anesthesiologists frequently give medications from multiple dose vials, many of which contain benzyl alcohol as a preservative. There is increasing concern that benzyl alcohol administration may be associated with "gasping syndrome," kernicterus, and intraventricular hemorrhage in premature neonates (1,2). Although it was originally believed that more than 99 mg/kg of benzyl alcohol must be administered to produce "gasping syndrome" (1), it has recently been suggested that *any* dose of benzyl alcohol administered to premature neonates may be associated with kernicterus and intraventricular hemorrhage (2). This had led to the recommendation that fluids containing benzyl alcohol be avoided when dealing with premature neonates (3).

The purpose of this letter is to draw attention to the fact that many medications commonly used in anesthesia contain benzyl alcohol. Some of these medications are listed together with their content of benzyl alcohol in Table 1. Alternatives to some of these medications can be used. Vecuronium powder (Organon) does not contain a preservative; however, the sterile water provided with it contains 9 mg/mL of benzyl alcohol. Vecuronium can be reconstituted instead with preservative-free water. Atracurium (Burroughs Wellcome) contains no preservatives when supplied in single dose ampuls.

Intravenous barbiturates (thiopental, thiamylal, and methohexital) are free of benzyl alcohol when reconstituted with preservative-free water or saline. Multiple dose ketamine, although free from benzyl alcohol, contains 0.1% benzethonium chloride, the effects of which have not been studied in premature neonates. Multiple dose vials of other drugs used in anesthesia (neostigmine, edrophonium, and lidocaine) do not contain benzyl alcohol but many contain other preservatives.

Administration during anesthesia of one or more of the drugs listed in Table 1 is by itself unlikely to present the premature neonate with a large benzyl alcohol load. However, premature neonates may also receive multiple other drugs in the neonatal intensive care unit, some of which may contain benzyl alcohol. As there may be no safe lower dose of benzyl alcohol in these patients, it would seem prudent to avoid the use of multiple dose vials containing benzyl alcohol whenever alternatives exist.

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References

1. Gershanik J, Boecler B, Ensley H, McCloskey S, George W. The gasping syndrome and benzyl alcohol poisoning. N Engl J Med 1982;307:1384–8.
2. Jardine DS, Rogers K. Relationships of benzyl alcohol to kernicterus, intraventricular hemorrhage, and mortality in preterm infants. Pediatrics 1989;83:153–60.
3. American Academy of Pediatrics, the Committee on Fetus and Newborn and the Committee on Drugs. Benzyl alcohol: toxic agent in neonatal units. Pediatrics 1983;72:356–7.

A Method of Securing Epidural Catheters

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL.

To the Editor:

The practitioner who inserts epidural catheters percutaneously is occasionally frustrated when the tape securing the catheter loses contact due to repeated shear forces caused by patient movement or as a result of perspiration accumulating under the tape. This can lead to dislodgement or kinking of the epidural catheter. Methods to prevent this include (a) painting the skin surface with tincture of benzoin to create better adhesion between the skin surface and tape; and (b) suturing the catheter to the skin. Suturing the catheter to the skin, in our experience, results both in occasional occlusion of the catheter secondary to overtight knots and in sutures cutting into the catheter wall, causing leaks.

We would like to describe a simple technique of securing epidural catheters to patient's skin utilizing two double stick disks (No. 2181, 3M Medical Surgical Division, St. Paul, Minn.) that are commonly used to hold precordial stethoscopes in place and are readily found in most anesthesia departments.

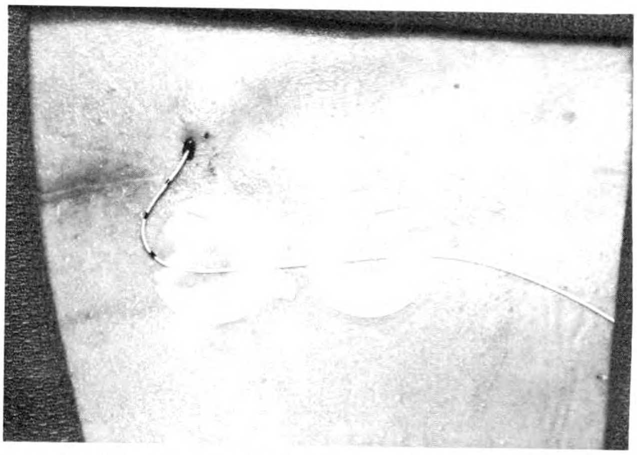

Figure 1. The patient is lying in the lateral position with the head to the right of the photograph. Double stick disks have been placed along the intended catheter route, and the catheter is placed in contact with the disks. The paper covering the double stick disks has been only partially removed, for illustrative purposes.

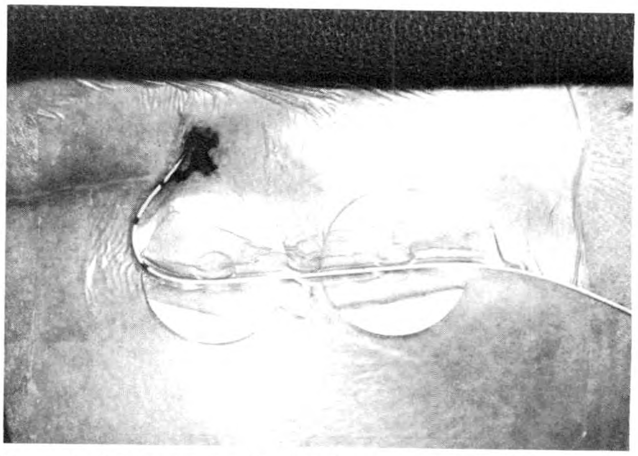

Figure 2. A transparent adhesive dressing covers the catheter, the double stick disks, and the catheter entry site.

After the placement of the catheter tip in the epidural space, the skin surrounding the point of entry of the catheter through the skin is painted with tincture of benzoin and allowed to dry. Two double stick disks with adhesive surfaces on both sides are then placed on the skin along the catheter's intended course, and the catheter is gently placed in contact with both disks (Figure 1). A 10 × 12-cm transparent adhesive dressing (No. 1626, 3M Medical Surgical Division) is then applied covering the catheter, the site of its entry through the skin, and both disks (Figure 2). Adhesive tape is applied over the remaining cephalad-directed catheter. This allows the easy visualization of the catheter insertion site and "sandwiches" the catheter between two adhesive surfaces, a maneuver that more securely maintains catheter position under the dressing and therefore decreases the possibility of catheter dislodgement.

This technique has been used successfully in more than 50 patients over a 6-mo period with no instance of catheter dislodgement. We have had instances where the edges of the transparent adhesive dressing have lifted off the skin, but in no patient was there lifting of the double stick disks from the skin, and the double stick disks prevented the dressing from coming off.

The only disadvantage to date has been encountered during dressing changes, because of difficulty in separating the adhesive "sandwich" from the catheter. We found it easier to carefully trim the adhesive dressing close to the catheter using scissors and apply new double stick disks to the skin before another transparent adhesive dressing is applied.

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Book Reviews

Anesthesia

W. S. Nimmo and G. Smith, eds. Boston: Blackwell Scientific Publications, 1989. 2 Vol, 1496 pp, $149.50.

Several anesthesia textbooks in English are now available to the anesthesia community. Should we procure every one of them or just select one that best fits our taste and needs? Of course, budgetary constraints are usually the determining factor. But if money is not an issue, I believe "the more, the merrier."

To make a point, I compared information on nitrous oxide in three modern anesthesia textbooks (Table 1). Clearly, each contains important bits of information that the other two do not. One feels the power of knowledge when several textbooks are under one's finger tips.

Nimmo and Smith's *Anaesthesia* is the most recent anesthesia textbook in English to come to light. Eighty-one chapters are written by 94 authors and organized into two volumes. The first volume primarily covers the scientific basis of anesthesia and general anesthesia. The second volume covers regional anesthesia, local anesthetics, pain management, and critical care.

The editors, in their preface, state that the "text was designed primarily . . . for anaesthetists preparing for the new final part of the FFARCS" and that the editors' aim was "to provide . . . virtually all the anaesthetic information required by a candidate." Some chapters are indeed very well written, informative, and exhaustive. These include chapters on the physiology of the heart, lung, kidney, and neuromuscular junction, as well as chapters on anesthesia for thoracic surgery, regional anesthesia, local anesthetics, and pain management. Other chapters, however, are less complete or contain controversial statements. Examples of one latter include the statement that the MAC of volatile anesthetic agents is lower in myxedema and higher in thyrotoxicosis (p 36) (MAC is independent of thyroid function; Anesthesiology 1968;19:1094) and that myasthenia gravis patients are sensitive to succinylcholine (p 797) (they are resistant to succinylcholine, although phase II block may appear earlier than usual; Anesthesiology 1988;69:760).

The brief chapter on immunology and anesthesia states repeatedly (pp 223, 227, 230) that "problems of an apparently immunological nature encountered by the anesthetist" include "the occurrence of postoperative infections and occasional rapid growth of metastases in the cancer patient." No references are offered in support of this statement. Eventually, the author of this chapter admits that the clinical significance of the changes in the immune system of the surgical patient is "dubious." But, he insists, "in certain situations [?] the changes may well allow rapid growth of opportunistic infections and metastatic growth" (p 230).

Several chapters lack important information. A table on antiarrhythmic drugs (p 615) omits calcium channel blockers. The section on obstetric anesthesia does not mention fetal monitoring. The metabolic rates of various volatile anesthetic agents and their byproducts could not be found. The section on hyperparathyroidism fails to mention the potential cardiac complications of hypercalcemia. The section on malignant hyperthermia (pp 790–1) neither mentions hypercarbia nor recommends that the patient in hyperthermic crisis be hyperventilated. The section on myasthenia gravis (p 797) does not mention the many reports on the safe use of nondepolarizing muscle relaxants in these patients. Despite numerous reports of serious and sometimes fatal complications after succinylcholine administration (Anesthesiology 1984;61:173), there is no warning regarding the use of this drug in patients with muscular dystrophy (p 800).

Chapter citations vary greatly, with important statements, some controversial, being made without revealing a

Table 1. Significant Facts About Nitrous Oxide, Each Found in Only One of the Three Anesthesia Textbooks

Effects of N_2O	Barash, Cullen, & Stoelting	Miller	Nimmo & Smith
Rate of increase in bowel gas volume	+	−	−
Rate of increase in pneumothorax volume	+	−	−
Rate of increase in tracheal tube cuff volume	−	+	−
Cardiovascular effects in hyperbaric chamber	−	−	+
"Antagonist" of ketamine anesthesia	−	−	+
Urethral sphincter tone during urodynamic studies	+	−	−

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source. For example, a statement that halothane inhibits histamine-induced bronchoconstriction for approximately 24 h after anesthesia is not referenced (p 43).

A particular problem for the American reader is the exclusive use of SI units. Although a common language for the scientific community is important, the fact remains that most American readers are not conversant with SI units. This reviewer would have preferred to see the editors empathize with their American cousins and include the alternate units to which American anesthesiologists are accustomed.

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Textbook of Pediatric Anesthetic Practice

E. Sumner and D. S. Hatch, eds. London: Baillière Tindall, 1989, 603 pp, $79.00.

This is a new textbook of pediatric anesthesia, edited by experienced physicians from The Hospital for Sick Children, Great Ormond Street, London. Although the list of contributors is an international one, the flavor of the practice described is that of the United Kingdom, providing a refreshing perspective for American readers. The editors' intent was to offer a text designed primarily for the general and trainee anesthetist, while perhaps serving as a reference for the specialist in pediatric anesthesia as well.

It is difficult to say which of these audiences is best served. The generalist will find that most aspects of modern pediatric anesthesia are discussed, with a fair sprinkling of clinically useful and practical advice. A number of topics, however, seem more geared to the specialist: anesthesia for pediatric liver, heart, and heart-lung transplantation are examples. Both audiences will likely be confused with the organization of the subject matter, for it is just not easy to predict where a given subject will be found. The index is sometimes helpful, but not consistently so, and one finds oneself paging through many sections to find a specific topic. The specialist may fare better here, being able to generate an educated guess as to where to look.

There are a number of chapters that are quite nicely done. The discussion of psychological preparation for surgery is practical and informed. The chapter on intravenous agents stresses the differences in pharmacokinetics found during development, providing a solid framework on which the individual drugs are considered. Similarly, muscle relaxants are presented with emphasis on age-related changes in actions and elimination; this section is especially well referenced.

The chapters on monitoring, neonatal physiology, cardiac disease, regional anesthesia, and postoperative care are all good, with a nice balance between clinical practicality and more in-depth consideration of basic concepts. Although caudal and epidural anesthetics are well covered, there is little discussion of spinal anesthesia, and no mention of neuraxial narcotics or patient-controlled analgesia i either of the latter two sections. I have to award four star to the chapters on liver and heart/heart-lung transplants They are brief but complete and clinically useful discussions of rather complex subjects. The chapter coverin "unusual conditions" has an extensive set of tables c congenital syndromes, organized by the body system affected, with particular attention to those syndromes wit congenital heart disease.

The remainder of the book is uneven in quality, wit some very good discussions and others that are less helpful. The chapter on fluid and electrolytes focuses excessively on major disturbances of hydration, and discusse the difficult areas of renal function, and fluid and electrolyte homeostasis in a confusing rather than illuminatin fashion. There is no consideration of parenteral nutrition Issues relating to intensive care are only peripherally discussed; there is only fleeting mention of extracorporea membrane oxygenation. The somewhat arbitrary organization of the subject material has the result that some topic are discussed in several sections (e.g., upper airway obstruction), whereas others are almost forgotten (scoliosis i the only orthopedic entity included, and it is found in th chapter on neurosurgical anesthesia).

Despite the above limitations, this book does indee review most aspects of contemporary pediatric anesthesi in a concise, timely, readable fashion. It successfully combines the practicality of a "handbook" with the depth of more expansive textbook. It will be a useful addition to th anesthesia library, where it will be consulted by the generalist and specialist alike.

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Cardiopulmonary Bypass: Current Concepts and Controversies

John N. Tinker, ed. Philadelphia: W. B. Saunders, 1989, 156 pp, $45.00.

Cardiopulmonary bypass (CPB), described by one of th authors here as "a pragmatic exercise in controlled pathophysiology," is one of the most common support procedures performed in the United States. Despite its successfu use for more than three decades, CPB practice varies widel and is accompanied by numerous gaps of knowledge an areas of controversy. This book attempts to define th known and explore the unknown.

The book is the third annual volume in the Society c Cardiovascular Anesthesiologists Monograph series. Thi teen authors from seven academic centers have crafte seven chapters that cover such topics as temperature an blood gases, effects of CPB on cerebral function, hemostasis, weaning from CPB, and the postperfusion syndrome

The title meets the high standards of its two predeces sors in the series. A wealth of information is offered in a brief, concise text. The chapters have extensive, up-to-date references, with a high of 180 and a low of 20, and in four other chapters ranging between 60 and 90. Tables and figures are uncluttered and well labeled and explained. Bold-faced phrases are used frequently to divide chapters into logical and manageable units, and the book has an adequate index. Finally, by today's ever-inflating standard, the book is modestly priced. A recent survey by the jobber Majors Scientific Books, Inc., showed that anesthesia texts distributed during the first 6 months of 1989 averaged more than $100 in cost. At $45, this book is a real bargain.

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Transplant Surgery: Anaesthesia and Perioperative Care (Volume 16, Monographs in Anaesthesiology)

J. V. Farman, ed. New York: Elsevier Science Publishing Co., 1988, 424 pp, $179.00.

The anesthetic and perioperative care of patients undergoing organ transplantation is a new, challenging, and rapidly growing area for anesthesiologists and intensivists. John Farman was a pioneer in transplantation anesthesiology, and the group of Cambridge authors he assembled for this book is one of the most experienced in the field. Thus, *Transplant Surgery: Anaesthesia and Perioperative Care* is a welcome addition to the limited references available. Although most subjects relevant to the perioperative care of transplant recipients are well covered in detail, additional information on two areas would have improved this book. First, the book's clinical information is based largely on the Cambridge group's experience. Although this is unquestionably valuable, more discussion of controversial clinical issues would have been welcome. Second, most of the information is drawn from the literature and practice related to kidney transplantation, and coverage of other types of transplantation is relatively limited.

The book's 17 chapters are organized in three sections: Basic Principles, The Donor, and Clinical Organ Transplantation. The first two chapters provide clear descriptions of the immunologic and pathologic phenomena of graft rejection, topics unfamiliar to most anesthesiologists. The next two chapters deal with immunosuppressive regimens and their complications and provide detailed descriptions of various infections and malignancy, although specific complications associated with each agent should have been included. "The Diagnosis of Death . . ." is an excellent and very informative chapter on the historical background, clinical signs, and tests that confirm brain death. The discussion of donor preparation includes donor selection criteria, nursing care, and administration of the brain-dead organ donor. Information on the pathophysiologic changes in the brain-dead patient should have been added as most health care personnel in peripheral hospitals, the most common organ procurement sites, are unfamiliar with this subject. The chapter on preservation of the donor organ clearly illustrates the basic principles of preservation.

The third section describes clinical management of transplantation of kidneys (three chapters), heart (two chapters), liver (three chapters), and pancreas, bone marrow, and other tissues (one chapter each). These chapters include indications, recipient preparation, surgical procedure, and anesthetic and postoperative care. The extensive coverage of kidney transplantation is a valuable reference.

In summary, this book is a welcome addition to the published information in a relatively new field. Anesthesiologists and trainees interested in organ transplantation will find this book a good reference, especially on immunology, brain death, organ preservation, and various aspects of kidney transplantation. For those beginning specialized anesthesia programs for transplantation of other organs, additional, more specific information will be required.

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Anesthesia and Analgesia

Index
Volume 69, 1989

Journal of the International Anesthesia Research Society

Author Index

Abdul-Rasool IH, Ward DS. Ventilatory and cardiovascular responses to sufentanil infusion in dogs anesthetized with isoflurane, 300
Abraham ZA, Lees DE. Two cardiac arrests after needle punctures in a patient with mitral valve prolapse: psychogenic?, 126
Acampora GA, Melendez JA, Keefe DL, Turnbull AD, Bedford RF. Intraoperative administration of the intravenous angiotensin-converting enzyme inhibitor, enalaprilat, in a patient with congestive heart failure, 833
Adkins MO, see Brodsky JB
Agoston S, see Swen J
Ahlf SB, see Roerig DL
Albin MS, see Karuparthy VR
Alexander CM, Teller LE, Gross JB. Pulse oximeters (letter, reply), 852
Amini SB, see Philipson EH
Anderton JM, see Sum-Ping ST
Armistead CW Jr, Vincent J-L, Preiser J-C, De Backer D, Le Minh T. Hypertonic saline solution-hetastarch for fluid resuscitation in experimental septic shock, 714
Arthur GR, see Feldman HS
Artru AA, Schultz AB, Bonneu JJ. Modification of an Eschmann Introducer to permit measurement of end-tidal carbon dioxide, 129
Artusio JF Jr, see Malhotra V
Ascher J, see Goldberg ME
Ashburn MA, see Stanley TH
Ashton-Miller JA, see Van Der Spek AFL
Atchison SR, Wedel DJ, Wilson PR. Effect of injection rate on level and duration of hypobaric spinal anesthesia, 496
Axelsson K, Nydahl P-A, Philipson L, Larsson P. Motor and sensory blockade after epidural injection of mepivacaine, bupivacaine, and etidocaine-a double-blind study, 739
Azad SS, see Goldberg ME
Azar I. (book review), 145, 858

Badenhorst E, see Coetzee A
Bailey PL
  CO_2 levels during opioid reversal with naloxone (letter), 420
  see Stanley TH
Bailey SL, see Parkinson SK
Baker PA, Schroeder D. Interpleural bupivacaine for postoperative pain during lactation, 400
Ballantyne JC, see Carr DB
Ballinger CM. (book review), 693
Barash PG, see Rosenbaum SH
Baribault J-P, see Lessard MR
Baron J-F, see Mouren S
Bashein G. (book review), 271
Bassoul B, see Eledjam JJ
Battito MF. The effect of fingerprinting ink on pulse oximetry (letter), 265
Beach TP, see Warner LO
Beavis RE. Effect of epinephrine on the duration of dibucaine (cinchocaine) spinal anesthesia, 819
Beck A, see Mayer N
Becker GL, see Landers DF
Bedford RF
  see Acampora GA
  see Long CW
Ben-David B, see Leighton BL
Benedetti C, see Khoury GF
Bengston A, see Bengston JP
Bengston JP, Bengston A, Sonander H, Stenqvist O. Humidity of the Bain and circle system reassessed, 83
Benson KT. The Jehovah's Witness patient: considerations for the anesthesiologist, 647
Benumof JL, see Gilbert D
Bernard J-M, Pinaud M, Maquin-Mavier I, Remi J-P, Passuti N. Hypotensive anesthesia with isoflurane and enflurane during total hip replacement: a comparative study of catecholamine and renin angiotensin responses, 467
Bernuau D, see Goldfarb G
Berry JM, Merin RG. Etomidate myoclonus and the open globe, 256
Bevan DR, see Smith CE
Bickler PE, Gold B, Johnson BH. Diffusion of felt-tip marker pen ink into intravenous bag (letter), 412
Biddle C. The Beelzebub nitrogen and preoxygenation (letter), 850
Bires JA, see Conterato JP
Birmingham PK, Stevenson GW, Uejima T, Hall SC. Isolated postoperative myoglobinuria in a pediatric outpatient-a case report of malignant hyperthermia, 846
Bissonnette B
  Sessler DI. Passive or active inspired gas humidification increases thermal steady-state temperatures in anesthetized infants, 783
  Sessler DI, LaFlamme P. Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature, 192
Bjoraker DG, see Koska AJ III
Blanchard J, see Karuparthy VR
Bloch EC, see Gorback MS
Blomberg S, Emanuelsson H, Ricksten S-E. Thoracic epidural anesthesia and central hemodynamics in patients with unstable angina pectoris, 558
Bloomfield P, see Scott DB
Bolliger C, see Coetzee A
Bonneu JJ, see Artru AA
Booij LHDJ, see Scheffer GJ
Borgeat A. Perioperative cardiovascular collapse in a patient previously treated with doxorubicin (letter, reply), 138
Bouletreau P, see Vedrinne C
Bourke DL, Silberberg MS, Ortega R, Willock MM. Respiratory responses associated with release of intraoperative tourniquets, 541
Bowler GMR, see Scott DB
Bradley EL Jr
  see Gregoretti S
  see Vinik HR
Bragg CL, Vukelich GR. Endotracheal tube extension for endobronchial intubation (letter), 548
Brajtbord D, see Brown MR
Brandom BW, see Law SC
Bredle D, see Reinhart K
Bremer DL, see Warner LO
Brochu JG, see Lessard MR
Brodsky JB, Adkins MO, Gaba DM. Bronchial cuff pressures of double-lumen tubes, 608
Bromley JJ, see Defalque RJ
Brousseau CA, see Lessard MR
Brown BR, see Frink EJ Jr
Brown MR
  Brajtbord D, Johnson DW, Ramsay MAE, Paulsen AW. Efficacy of oral cyclosporine given prior to liver transplantation, 773
  see Ramsay MAE
Brown P, see Goldman JM
Brugada J, see Eledjam JJ
Brull SJ, Greene NM. Time-courses of zones of differential sensory blockade during spinal anesthesia with hyperbaric tetracaine or bupivacaine, 342
Brussel T, Theissen JL, Vigfusson G, Lunkenheimer PP, Van Aken H, Lawin P. Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol, 35
Bubbers S, see Stanley TH
Burgess FW, Wilcosky B Jr. Thoracic epidural anesthesia for transsternal thymectomy in myasthenia gravis, 529
Burton P, Kurinczuk J, De Melo E. "Statistical power" and

interpretation of small studies: does atracurium pretreatment reduce the incidence of succinylcholine fasciculations? (letter), 263

Camann W, Huckaby T. Disposal of epidural catheter stylets: taming the snake (letter), 411
Campbell FW, see Jobes DR
Candeletti S, Ferri S. Clinical use of subarachnoid neuropeptides: an experimental contribution (letter), 416
Canet J, Ricos M, Vidal F. Early postoperative arterial oxygen desaturation-determining factors and response to oxygen therapy, 207
Carapetis RJ, see Nancarrow C
Carr DB, Ballantyne JC, Osgood PF, Kemp JW, Szyfelbein SK. Pituitary-adrenal stress response in the absence of brain-pituitary connections, 197
Carter A, see Rudo FG
Carter JG, see Pearson KS
Chang J-L, see Navalgund AA
Chen L, see Prasad KK
Coetzee A
  Fourie P, Bolliger C, Badenhorst E, Rebel A, Lombard C. Effect of N_2O on segmental left ventricular function and effective arterial elastance in pigs when added to a halothane-fentanyl-pancuronium anesthetic technique, 313
  Fourie P, Coetzee J, Badenhorst E, Rebel A, Bolliger C, Uebel R, Wium C, Lombard C. Effects of various propofol plasma concentrations on regional myocardial contractility and left ventricular afterload, 473
Coetzee J, see Coetzee A
Coldwell DM, see Loper KA
Collins JG
  see Murata K
  see Nishio Y
Colonna-Romano P, Shapiro BE. Unintentional dural puncture and prophylactic epidural blood patch in obstetrics, 522
Concepcion MA, Lambert DH. Tourniquet pain during bupivacaine and tetracaine spinal anesthesia (letter, reply), 411
Conterato JP, Lindahl SGE, Meyer DM, Bires JA. Assessment of spontaneous ventilation in anesthetized children with use of a pediatric circle or a Jackson-Rees system, 484
Cook DR, see Law SC
Coppel DL, see Dwyer R
Coté JJ, see Lessard MR
Cottrell JE, see Hartung J
Coursin DB, Klasek G, Goelzer SL. Increased requirements for continuously infused vecuronium in critically ill patients, 518
Coveler LA, Lester RC. Contaminated oxygen cylinder, 674
Coventry DM, Todd G. Epidural clonidine in lower limb deafferentation pain (letter), 424
Covino BG, see Feldman HS
Cronau LH, see Stanley TH
Crosby G, see Szabo MD
  see Ho LC
  see Szabo G
Cuplin S, see Ready LB

Dalens B
  Tanguy A, Vanneuville G. Lumbar plexus blocks and lumbar plexus nerve blocks (letter), 852
  Vanneuville G, Dechelotte P. Penile block via subpubic space in 100 children, 41
  Vanneuville G, Tanguy A. Comparison of the fascia iliaca compartment block with the 3-in-1 block in children, 705
Davidson PJ, see Warner LO
Davis JR, see Frink EJ Jr
Davis RF
  (book review), 146
  Sidi A. Effect of isoflurane on the extent of myocardial necrosis and on systemic hemodynamics, regional myocardial blood flow, and regional myocardial metabolism in dogs after coronary artery occlusion, 575
Dawson CA, see Roerig DL
De Backer D, see Armistead CW Jr
de Jong RH. (book review), 270
De La Coussaye JE, see Eledjam JJ
De Melo E, see Burton P
De Soto H, Turk P. Cimetidine in anaphylactic shock refractory to standard therapy (letter), 264
Dechelotte P, see Dalens B
Defalque RJ, Bromley JJ. Poststernotomy neuralgia: a new pain syndrome, 81; (letter, reply 692)
Denault PH, see Lessard MR
Denson DD. Time-dependent changes in bupivacaine pharmacokinetics (letter), 423
Dershwitz M, Sréter FA, Ryan JF. Ketamine does not trigger malignant hyperthermia in susceptible swine, 501
DeSimone CA, see Leighton BL
Di Martino MR, see Peduto VA
Diaz JH. (book review), 695
Didier P, see Hofer RE
DiFazio CA, see Stone DJ
DiGiovanni DA, see Frink EJ Jr
Dimick A, see Gregoretti S
Dinner M. Monitoring effective chest compression during cardiopulmonary resuscitation (letter), 418
Dohi S, see Takeshima R
Domar AD, Everett LL, Keller MG. Preoperative anxiety: is it a predictable entity?, 763
Donati F, see Smith CE
Dorsey MJ, Jones BR. An inexpensive, disposable adapter for increasing the safety of blind nasotracheal intubations (letter), 135
dos Reis A Jr. Tourniquet use and intraoperative hypothermia (letter), 549
Dowling C, see Loper KA
Downing JW, see Karuparthy VR
Drenger B, Magora F. Urodynamic studies after intrathecal fentanyl and buprenorphine in the dog, 348
Drummond GB, see Duggan JE
Dubin SA, Silverstein PI, Wakefield ML, Jense HG. Comparison of the effects of oral famotidine and ranitidine on gastric volume and pH, 680
Duggan JE, Drummond GB. Abdominal muscle activity and intraabdominal pressure after upper abdominal surgery, 598
Duncan PG, see Lang SA
Dupuis PR, see Lang SA
Durrani Z. "Sciatic radicular pain" or piriformis muscle syndrome? (letter), 260
Dwyer R, Coppel DL. Intravenous injection of liquid halothane, 250
Dzelzkalns RR, see Stanley TH

East KA, see Stanley TH
Ebert TJ, Kampine JP. Nitrous oxide augments sympathetic outflow: direct evidence from human peroneal nerve recordings, 444
Edmondson R, Del Valle O, Shah N, Wong G, Dwyer D, Matarazzo D, Thorne A, Coffey C, Bedford R. Esmolol for potentiation of nitroprusside-induced hypotension-impact on the cardiovascular, adrenergic, and renin-angiotensin systems in man, 202
Eger EI II
  see Gauntlett IS
  see Targ AG
  see Yasuda N
Eisele JH, see Hanowell LH
Elam M, see Lundin S
Eledjam JJ, De La Coussaye JE, Brugada J, Bassoul B, Gagnol JP, Fabregat JR, Massé C, Sassine A. In vitro study on mechanisms of bupivacaine-

induced depression of myocardial contractility, 732
Ellison N
  (book review), 145
  see Jobes DR
Emanuelsson H, see Blomberg S
Enoki T, Naito Y, Hirokawa Y, Nomura R, Hatano Y, Mori K. Marked sensitivity to pancuronium in a patient without clinical manifestations of myasthenia gravis, 840
Erskine EV, see Hanowell LH
Everett LL, see Domar AD
Evers AS, see Stern RC
Eyrich K, see Reinhart K

Fabregat JR, see Eledjam JJ
Fagan D
  see Lee A
  see Scott DB
Fahey MR, see Gauntlett IS
Fassoulaki A, Pamouktsoglou P. Prolonged nasotracheal intubation and its association with inflammation of paranasal sinuses, 50
Faubert PR. Pulse oximeters (letter), 851
Feldman HS, Arthur GR, Covino BG. Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine, and lidocaine in the conscious dog, 794
Feldman SA, Soni N, Kraayenbrink MA. Effect of rate of injection on the neuromuscular block produced by vecuronium, 624
Feldmann G, see Goldfarb G
Ferri S, see Candeletti S
Fibuch EE, Opper SE. Back pain following epidurally administered nesacaine-MPF, 113
Finch JS, see Kennedy TP
Fink BR, Walker S. Orientation of fibers in human dorsal lumbar dura mater in relation to lumbar puncture, 768
Finster M, see Pedersen H
Flacke JW, see Mills CA
Flacke WE, see Mills CA
Foehring U, see Reinhart K
Ford RD, see Rudo FG
Fourie P, see Coetzee A
Fragen RJ. What is MIR? (letter), 413
Frink EJ Jr, DiGiovanni DA, Davis JR, Brown BR. Serum ammonia levels in response to glycine infusion in normal and cirrhotic rats, 776
Fujita Y, Sakai T, Ohsumi A, Takaori M. Effects of hypokapnia and hypercapnia on splanchnic circulation and hepatic function in the beagle, 152

Gaba DM, see Brodsky JB
Gagnol JP, see Eledjam JJ
Gallen JS. Aminophylline reversal of midazolam sedation (letter), 268
Garla PGN, see Price JA
Gauntlett IS, Koblin DD, Fahey MR, Konopka K, Gruenke LD, Waskell L, Eger EI II. Metabolism of isoflurane in patients receiving isoniazid, 245
Gebauer C, see Goldfarb G
Gebershagen HU, see Lang E
Gelman S
  Carbon dioxide and hepatic circulation (editorial), 149
  see Gregoretti S
Gibbons JJ. Tourniquet pain during bupivacaine and tetracaine spinal anesthesia (letter), 410
Gielen M, see Stienstra R
Gieraerts R, see Navalgund AA
Gilbert D, Benumof JL. Biphasic carbon dioxide elimination waveform with right mainstem bronchial intubation, 829
Gild W. (book review), 694
Gissen AJ. (book review), 147
Gitelman DR, see Young WL
Glendrange RR, see Orlin SE
Goelzer SL, see Coursin DB
Gold B, see Bickler PE
Goldberg ME
  Larijani GE, Azad SS, Sosis M, Seltzer JL, Ascher J, Weakly JN. Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients, 93
  see Norris MC
Golden WE, see Lavender RC
Goldfarb G, Rogier E, Gebauer C, Lassen C, Bernuau D, Jolis P, Feldmann G. Comparative effects of halothane and isoflurane anesthesia on the ultrastructure of human hepatic cells, 491
Goldman JM, Brown P. (book review), 695
Gomez MN, see Pearson KS
Gomillion MC, see Malhotra V
Gonce S, see Waymack JP
Gorback MS
  Cut-off values and aspiration risk (letter), 417
  Quill TJ, Bloch EC, Graubert DA. Oscillometric blood pressure determination from the adult thumb using an infant cuff, 668
Goucke R. Hazards of henna (letter), 416
Grady IP, see Long WB
Graubert DA, see Gorback MS
Gravlee GP. Limit(ation)s for ACT (letter, reply), 143
Green Larach M. Standardization of the caffeine halothane muscle contracture test, 511
Greene NM, see Brull SJ
Gregoretti S, Gelman S, Dimick A, Bradley EL Jr. Hemodynamic changes and oxygen consumption in burned patients during enflurane or isoflurane anesthesia, 431
Grimbergen CA, see Scheffer GJ
Gronert GA, see Melton AT
Gross JB, see Alexander CM
Grover VK, Sharma S. Nitroglycerine, succinylcholine and intraocular pressure (letter, reply), 141
Gruenke LD, see Gauntlett IS
Gualtieri JF, see Roerig DL
Guiraud M, see Vedrinne C
Gungui P, see Peduto VA
Gunter JB. A buccal sensor for measuring arterial oxygen saturation (letter), 417

Haasio J, see Heavner JE
Hag B, see Mouren S
Hague B
  see Stanley TH
  see Streisand JB
Hall SC, see Birmingham PK
Halldin M, see Lee A
Hanowell LH, Eisele JH, Erskine EV. Autotransfusor removal of fentanyl from blood, 239
Harioka T, Stone T, Toda H, Miyake C. Malignant hyperthermia in a hemodialysis patient, 119
Harmon TW, see Pedersen H
Hartung J, Cottrell JE. On hot mice, cold facts, and would-be replication (letter), 408
Haschke RH, see Ready LB
Hatano Y, see Enoki T
Heavner JE, Leinonen L, Haasio J, Kytta J, Rosenberg PH. Interaction of lidocaine and hypothermia in Bier blocks in volunteers, 53
Heerdt PM, Yee LL. Differential effect of prostaglandin E_2 and sodium nitroprusside on intrapulmonary shunt fraction in a cardiac transplantation patient, 665
Hennes HJ, see Jantzen JP
Henriksen JH, see Mogensen T
Hermans J, see Swen J
Hetherington RG, McQuillan PM. Venous air embolism during hip arthrography (letter), 264
Hickey PR. Perioperative cardiovascular collapse in a patient previously treated with doxorubicin (letter), 138
Hipkins SF, see Nancarrow C
Hirner A, see Reinhart K
Hirokawa Y, see Enoki T

- Ho GH, see Streisand JB
- Ho LC, Crosby G, Sundaram P, Ronner SF, Ojemann RG. Ulnar train-of-four stimulation in predicting face movement during intracranial facial nerve stimulation, 242
- Hofer RE, Lennon RL, Didier P. "Just a little bit more" (letter), 691
- Hoffman WE. The effect of fentanyl on basal and stimulated plasma levels of atrial natriuretic peptide (letter, reply), 549
- Hoffmann CO, Swanson GA. Oral reinforced endotracheal tube crushed and perforated from biting (letter), 552
- Hogan KJ, Rusy D, Springman SR. Difficult laryngoscopy and diabetes mellitus (letter, reply), 419, 550
- Hoka S, Sato M, Yoshitake J, Kukita J. Management of a newborn infant with congenital laryngeal atresia, 535
- Holley HS, see Scheffer GJ
- Holm BA, Matalon S. The role of pulmonary surfactant in the development and treatment of adult respiratory distress syndrome, 805
- Huckaby T, see Camann W
- Husain FJ, see Karuparthy VR
- Hynynen M. The effect of fentanyl on basal and stimulated plasma levels of atrial natriuretic peptide (letter), 549

- Ilsey AH, see Rutten AJ
- Ivankovich AD, see Tuman KJ

- Jahr J, see Navalgund AA
- James TN. A cardiogenic hypertensive chemoreflex, 633
- Jantzen JP, Hennes HJ, Wallfenfang T. Nitroglycerine, succinylcholine and intraocular pressure (letter), 139
- Jarvis AP, see Skues MA
- Jayagopal S, see Tagliente TM
- Jense HG, see Dubin SA
- Jobes DR, Ellison N, Campbell FW. Limit(ation)s for ACT (letter), 142
- Johnson BH, see Bickler PE
- Johnson DW, see Brown MR
- Johnson KJ, see Kennedy TP
- Johnston WE, see Prough WE
- Jolis P, see Goldfarb G
- Jones BR, see Dorsey MJ
- Jonges R, see Scheffer GJ

- Kagiya M, see Kochi T
- Kamaya H, see Nosaka S
- Kampine JP
  - see Ebert TJ
  - see Roerig DL
  - see Schmeling WT
- Kandall SR, see Topsis J
- Kang Y. (book review), 860
- Karambelkar D, see Melnick B
- Karuparthy VR, Downing JW, Husain FJ, Knape KG, Blanchard J, Solomon D, Albin MS. Incidence of venous air embolism during cesarean section is unchanged by the use of a 5 to 10° head-up tilt, 620
- Keefe DL, see Acampora GA
- Kehlet H, see Mogensen T
- Keller MG, see Domar AD
- Kelly JS, Royster RL. Noninvasive transcutaneous cardiac pacing, 229
- Kemp JW, see Carr DB
- Kennedy RW, Till W, Shah JB. Imprecise fentanyl and sufentanil labels (letter), 137
- Kennedy TP, Johnson KJ, Kunkel RG, Ward PA, Knight PR, Finch JS. Acute acid aspiration lung injury in the rat: biphasic pathogenesis, 87
- Kersting T, see Reinhart K
- Ket JM, see Swen J
- Khoury GF, Benedetti C. T-wave changes associated with electroconvulsive therapy, 677
- Kien ND, see Melton AT
- Kinas HY, see Topsis J
- King H-K, Wooten DJ. Blind nasal intubation by monitoring end-tidal CO_2 (letter), 412
- Kissin I
  - Xavier AV, McDanal J. Blockade of sciatic nerve branches relieves sciatic radicular pain (letter), 262
  - see Vinik HR
- Kitahata LM
  - see Murata K
  - see Nishio Y
- Klain M, see Wilks DH
- Klasek G, see Coursin DB
- Knape KG, see Karuparthy VR
- Knight PR, see Kennedy TP
- Koblin DD, see Gauntlett IS
- Kochi T, Hagiya M, Mizuguchi T. Effects of enflurane on contractile responses of canine trachealis muscle, 60
- Konopka K, see Gauntlett IS
- Koot HWJ, see Swen J
- Koska AJ III, Bjoraker DG. An anesthetic adapter for all metered inhalers is readily available (letter), 266
- Kotrly KJ, see Roerig DL
- Kraayenbrink MA, see Feldman SA
- Krainick JU, see Lang E
- Kroon JW, see Stienstra R
- Krupin T, see Orlin SE
- Kuhnert BR, see Philipson EH
- Kukita J, see Hoka S
- Kumeta Y, see Murata K
- Kunkel RG, see Kennedy TP
- Kupferberg JP, see Roth S
- Kurata FK, see Orlin SE
- Kurinczuk J, see Burton P
- Kutcher BA, see Rudo FG
- Kvalheim L, see Reiestad F
- Kytta J, see Heavner JE

- LaFlamme P, see Bissonnette B
- Lambert DH, see Concepcion MA
- Lamont M, see Lee A
- Lampert BA. Multiple nerve palsies after anesthesia-a complication of nitrou oxide use? (letter), 136
- Landers DF
  - Becker GL, Wong KC. Calcium, calmodulin, and anesthesiology, 1
  - Newland MC, Wolpert L. Pulse oximetry probe disconnection (letter), 265
- Lang E, Krainick JU, Gerbershagen HU. Spinal cord transmission of impulses during high spinal anesthesia as measured by cortical evoked potentials, 15
- Lang SA, Duncan PG, Dupuis PR. Fatal air embolism in an adolescent with Duchenne muscular dystrophy during Harrington instrumentation 132
- Larijani GE, see Goldberg ME
- Larsson P, see Axelsson K
- Lassen C, see Goldfarb G
- Lavender RC, Salmon JS, Golden WE. Pseudothrombocytopenia in an elderly preoperative patient, 396
- Law SC, Ramzan IM, Brandom BW, Cool DR. Intravenous ranitidine antagonizes intense atracurium-induced neuromuscula blockade in rats, 611
- Lawin P, see Brüssel T
- Le Minh T, see Armistead CW Jr
- Lecky J, see Loper KA
- Lee A
  - Fagan D, Lamont M, Tucker GT, Halldin M, Scott DB. Disposition kinetics of ropivacaine in humans, 736
  - see Scott DB
- Lee YJ, see Pantuck EJ
- Lees DE, see Abraham ZA
- Leighton BL, De Simone CA, Norris MC, Ben-David B. Intrathecal narcotics for labor revisited: the combination of fentanyl and morphine intrathecally provides rapid onset profound, prolonged analgesia, 1
- Leiman BC, see Stanley TH
- Leinonen L, see Heavner JE
- Lell WA, Wright AJ. (book review), 859
- Lennon RL, see Hofer RE
- Lessard MR, Trépanier CA, Baribault J-P, Brochu JG, Brousseau CA, Coté JJ, Denault PH. Isoflurane-induced

hypotension in orthognathic surgery, 379
Lester RC, see Coveler LA
Lindahl SGE, see Conterato JP
Little WL, see Parkinson SK
Lombard C, see Coetzee A
Long CW, Shah NK, Loughlin C, Spydell J, Bedford RF. A comparison of EEG determinants of near awakening from isoflurane and fentanyl anesthesia-spectral edge, median power frequency, and γ ratio, 169
Long WB, Rosenblum S, Grady IP. Successful resuscitation of bupivacaine-induced cardiac arrest using cardiopulmonary bypass, 403
Loper KA
  Coldwell DM, Lecky J, Dowling C. Celiac plexus block for hepatic arterial embolization: a comparison with intravenous morphine, 398
  Ready LB, Nessly M, Rapp SE. Epidural morphine provides greater pain relief than patient-controlled intravenous morphine following cholecystectomy, 826
Loughlin C, see Long CW
Lundh R, see Scott DB
Lundin S, Wallin BG, Elam M. Intraneural recording of muscle sympathetic activity during epidural anesthesia in humans, 788
Lunkenheimer PP, see Brüssel T

MacIntyre PE, see Slee TA
Maekawa N, see Sugiyama D
Magora F, see Drenger B
Malhotra V, Gomillion MC, Artusio JF Jr. Hemoptysis in a child during extracorporeal shock wave lithotripsy, 526
Maquin-Mavier I, see Bernard J-M
Marcus MA, see Stanley TH
Martin JT. Postoperative isolated dysfunction of the long thoracic nerve: a rare entity of uncertain etiology, 614
Martucci RW, see Melton AT
Marty J, Reves JG. Cardiovascular control mechanisms during anesthesia (editorial), 273
Massé C, see Eledjam JJ
Matalon S, see Holm BA
Mather LE
  see Nancarrow C
  see Rutten AJ
Mayer N, Zimpfer M, Raberger G, Beck A. Fentanyl inhibits the canine carotid chemoreceptor reflex, 756
Mayes GA. Thiamine for prevention of Wernicke's encephalopathy: a reminder (letter), 407
Mazoit JX. Time-dependent changes in bupivacaine pharmacokinetics (letter, reply), 424
McCarthy RJ, see Tuman KJ
McDanal J, see Kissin I
McIlvaine WB, see Reiestad F
McLean CF, see Nancarrow C
McMechan FH, McMechan L. Elmer Isaac McKesson, MD, Anesthetist: his life and work: 1937;16:1-6 (historical note), 259
McMechan L, see McMechan FH
McQuillan PM, see Hetherington RG
Mehta MP, see Sum-Ping ST
Melendez JA, see Acampora GA
Melnick B, Sawyer R, Karambelkar D, Phitayakorn P, Uy NTL, Patel R. Delayed side effects of droperidol after ambulatory general anesthesia, 748
Melton AT, Martucci RW, Kien ND, Gronert GA. Malignant hyperthermia in humans-standardization of contracture testing protocol, 437
Merin RG, see Berry JM
Meyer DM, see Conterato JP
Meyer RM. Difficult intubation in severe diabetes (letter), 419
Milde LN
  An anaphylactic reaction to fibrin glue, 684
  On hot mice, cold facts, and would-be replication (letter, reply), 410
Miller JD, see Mills CA
Mills CA, Flacke JW, Miller JD, Flacke WE. CO_2 levels during opioid reversal with naloxone (letter, reply), 421
Miskell P, see Waymack JP
Miyake C, see Harioka T
Mizuguchi T, see Kochi T
Mock DL, see Stanley TH
Mogensen T, Simonsen L, Scott NB, Henriksen JH, Kehlet H. Tachyphylaxis associated with repeated epidural injections of lidocaine is not related to changes in distribution or the rate of elimination from the epidural space, 180
Mori K, see Enoki T
Mouren S, Baron J-F, Hag B, Arthaud M, Viars P. Normovolemic hemodilution and lumbar epidural anesthesia, 174
Moyers JR, see Gomez MN
Mueller JB, see Parkinson SK
Murata K, Nakagawa I, Kumeta Y, Kitahata LM, Collins JG. Intrathecal clonidine suppresses noxiously evoked activity of spinal wide dynamic neurons in cats, 185

Naito Y, see Enoki T
Nakagawa I, see Murata K
Nancarrow C
  Rutten AJ, Runciman WB, Mather LE, Carapetis RJ, McLean CF, Hipkins SF. Myocardial and cerebral drug concentrations and the mechanisms of death after fatal intravenous doses of lidocaine, bupivacaine, and ropivacaine in the sheep, 276
  see Rutten AJ
Napoleone M, see Peduto VA
Navalgund AA, Jahr J, Gieraerts R, Chang J-L, Price GS, Garla PGN. Multiple nerve palsies after anesthesia-a complication of nitrous oxide use? (letter, reply), 137
Neill P, Sleigh JW. Ether does not antagonize bronchoconstriction caused by acetylcholine, histamine, or phenylephrine, 226
Nessly M
  see Loper KA
  see Ready LB
Newland MC, see Landers DF
Nishio Y, Sinatra RS, Kitahata LM, Collins JG. Spinal cord distribution of ^{3}H-morphine after intrathecal administration: relationship to analgesia, 523
Nobuhara K, Sugiyama D
Nomura R, see Enoki T
Norris MC
  Goldberg ME. The Beelzebub nitrogen and preoxygenation (letter, reply), 851
  see Leighton BL
Nosaka S, Kamaya H, Ueda I, Wong KC. Smooth muscle contraction and local anesthetics: calmodulin-dependent myosin light-chain kinase, 504
Nugent M, see Reves JG
Nydahl P-A, see Axelsson K

Obara H, see Sugiyama D
Ogin GA. Pseudosciatica (letter), 261
Ohsumi A, see Fujita Y
Ojemann RG, see Ho LC
Opper SE, see Fibuch EE
Orlin SE, Kurata FK, Krupin T, Schneider M, Glendrange RR. Ocular lubricant and corneal injury during anesthesia, 384
Ortega R, see Bourke DL
Osgood PF, see Carr DB
Ossipov M, see Rudo FG

Pace NL, see Stanley TH
  see Stanley TH
  see Streisand JE
Paglia SL, Sommer RM. AIDS infection protection-reinforced gloves (letter), 407
Pamouktsoglou P, see Fassoulaki A

- Pantuck CB, see Pantuck EJ
- Pantuck EJ, Weissman C, Pantuck CB, Lee YJ. Effects of parenteral amino acid nutritional regimens on oxidative and conjugative drug metabolism, 727
- Parker EO. Epidural narcotic use for outpatient pain treatment (letter), 408
- Parkinson SK, Mueller JB, Little WL, Bailey SL. Lumbar plexus blocks and lumbar plexus nerve blocks (letter, reply), 854
- Pascucci RC. (book review), 859
- Passuti N, see Bernard J-M
- Patel R, see Melnick B
- Patricot MC, see Vedrinne C
- Paulsen AW, see Brown MR
- Pavlin EG, see Slee TA
- Pearson KS, Gomez MN, Moyers JR, Carter JG, Tinker JH. A cost/benefit analysis of randomized invasive monitoring for patients undergoing cardiac surgery, 336
- Pedersen H, Santos AC, Steinberg ES, Schapiro HM, Harmon TW, Finster M. Incidence of visceral pain during cesarean section: the effect of varying doses of spinal bupivacaine, 46
- Peduto VA, Gungui P, Di Martino MR, Napoleone M. Accidental subarachnoid injection of pancuronium, 516
- Peper A, see Scheffer GJ
- Perel A, see Segal E
- Pettersen B, see Reiestad F
- Philipson EH, Kuhnert BR, Pimentel R, Amini SB. Transient maternal hypotension following epidural anesthesia, 604
- Philipson L, see Axelsson K
- Phitayakorn P, see Melnick B
- Pimentel R, see Philipson EH
- Pinaud M, see Bernard J-M
- Pollan S, Tadjziechy M. Esmolol in the management of epinephrine and cocaine-induced cardiovascular toxicity, 663
- Prasad KK, Chen L. Anesthetic management of a patient with bullous pemphigoid, 537
- Preiser J-C, see Armistead CW Jr
- Price GS, see Navalgund JA
- Prohovnik I, see Young WL
- Prough DS, Johnston WE. Fluid resuscitation in septic shock (editorial), 699
- Prys-Roberts C, see Skues MA

- Quarmby R, Schmitt L. A simple, inexpensive device to prevent airway disconnection when using remote capnometry (letter), 414
- Quill TJ, see Gorback MS
- Quinlan JJ. (book review), 696

- Raberger G, see Mayer N
- Radošević-Stašić B, Udovic-Sirola M, Stojanov L, Ribaric L, Rukavina D. Growth of allogeneic sarcoma in mice subjected to halothane anesthesia and/or surgical stress, 570
- Ramsay MAE
  - Takaoka F, Brown MR, Rosenlöf P. Coronary artery vasospasm following placement of a cold liver graft during orthotopic liver transplantation (letter), 854
  - see Brown MR
- Ramzan IM, see Law SC
- Rapp SE, see Loper KA
- Rashkovsky OM, see Swen J
- Rawal N, see Stanley TH
- Ready LB
  - Cuplin S, Haschke RH, Nessly M. Spinal needle determinants of rate of transdural fluid leak, 457
  - see Loper KA
- Rebel A, see Coetzee A
- Reiestad F
  - McIlvaine WB. Interpleural anesthesia for extracorporeal shock wave lithotripsy (letter), 551
  - McIlvaine WB, Kvalheim L, Stokke T, Pettersen B. Interpleural analgesia in treatment of upper extremity reflex sympathetic dystrophy, 671
- Reinhart K, Foehring U, Kersting T, Schaefer M, Bredle D, Hirner A, Eyrich K. Effects of thoracic epidural anesthesia on systemic hemodynamic function and systemic oxygen supply-demand relationship, 360
- Remi J-P, see Bernard J-M
- Reves JG
  - Nugent M. New directions in anesthesia subspecialty training? (editorial), 1
  - see Marty J
- Reynolds PI
  - Wilton NC. Inadvertent benzyl alcohol administration in neonates: do we contribute? (letter), 855
  - see Van Der Spek AFL
- Ribaric L, see Radošević-Stašić B
- Richards MJ, see Skues MA
- Ricksten S-E, see Blomberg S
- Ricos M, see Canet J
- Rics SA, see Truog RD
- Roerig DL, Kotrly KJ, Dawson CA, Ahlf SB, Gualtieri JF, Kampine JP. First-pass uptake of verapamil, diazepam, and thiopental in the human lung, 461
- Rogers GL, see Warner LO
- Rogier E, see Goldfarb G
- Ronner SF, see Ho LC
- Rorie DK. (book review), 271
- Ros HH, see Scheffer GJ
- Rosenbaum SH, Barash PG. Is anesthesia therapeutic? (editorial), 555
- Rosenberg H. Standards for halothane/caffeine contracture test (editorial), 429
- Rosenberg PH, see Heavner JE
- Rosenblum S, see Long WB
- Rosenlöf P, see Ramsay MAE
- Roth S, Kupferberg JP. Adverse responses following intraoperative administration of orthoclone OKT3, 822
- Rovenstine EA. Anesthesia: organization for teaching. Anesthesia and Analgesia: 1937;16:318-22 (historical note), 118
- Royster RL, see Kelly JS
- Rudo FG, Wynn RL, Ossipov M, Ford RD, Kutcher BA, Carter A, Spaulding TC. Antinociceptive activity of pentamorphone, a 14-β-aminomorphinone derivative, compared to fentanyl and morphine, 450
- Rukavina D, see Radošević-Stašić B
- Runciman WB
  - see Nancarrow C
  - see Rutten AJ
- Rusy D, see Hogan KJ
- Rutten AJ
  - Nancarrow C, Mather LE, Ilsey AH, Runciman WB, Upton RN. Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine, and ropivacaine in sheep, 291
  - see Nancarrow C
- Ryan JF, see Dershwitz M

- Sakai T, see Fujita Y
- Salmon JS, see Lavender RC
- Santos AC, see Pedersen H
- Sassine A, see Eledjam JJ
- Sato M, see Hoka S
- Sawyer R, see Melnick B
- Schaefer M, see Reinhart K
- Schapiro HM, see Pedersen H
- Scheffer GJ, Jonges R, Holley HS, Grimbergen CA, Ros HH, Peper A, Booij LHDJ. Effects of halothane on the conduction system of the heart in humans, 721
- Schmeling WT, Kampine JP, Warltier DC. Negative chronotropic actions of sufentanil and vecuronium in chronically instrumented dogs pretreated with propranolol and/or diltiazem, 4
- Schmitt L, see Quarmby R
- Schmitt LG, Ullman DA. A method of

securing epidural catheters (letter), 856
Schneider M, see Orlin SE
Schork MA, see Van Der Spek AFL
Schroeder D, see Baker PA
Schultz AB, see Artru AA
Scott DB
  Regional anesthesia for pediatric surgery (editorial), 697
  Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine, 563
  see Lee
Scott NB, see Mogensen T
Segal E, Perel A. Heart synchronized ventilation during extracorporeal shock wave lithotripsy (letter), 139
Seitman DT, Shapiro BE. Inability to thread epidural catheter through epidural needle (letter), 267
Seltzer JL, see Goldberg ME
Sessler DI, see Bissonnette B
Shah JB, see Kennedy RW
Shah NK, see Long CW
Shapiro BE
  see Colonna-Romano P
  see Seitman DT
Sharer SR, see Slee TA
Sharma S, see Grover VK
Shay S, see Whelan E
Sidi A, see Davis RF
Silberberg MS, see Bourke DL
Silverstein PI, see Dubin SA
Simonsen L, see Mogensen T
Sinatra RS, see Nishio Y
Skues MA, Richards MJ, Jarvis AP, Prys-Roberts C. Preinduction atropine and glycopyrrolate and hemodynamic changes associated with induction and maintenance of anesthesia with propofol and alfentanil, 386
Slee TA, Sharar SR, Pavlin EG, MacIntyre PE. The effects of airway impedence on work of breathing during halothane anesthesia, 374
Sleigh JW, see Neill P
Smith CE, Donati F, Bevan DR. Effects of succinylcholine at the masseter and adductor pollicis muscles in adults, 158
Smith RT. Smithisms (letter), 141
Solomon D, see Karuparthy VR
Sommer RM, see Paglia SL
Sonander H, see Bengston JP
Soni N, see Feldman SA
Sosis M, see Goldberg ME
Sosnowski M, Yaksh TL. Role of spinal adenosine receptors in modulating the hyperesthesia produced by spinal glycine receptor antagonism, 587
Spaulding TC, see Rudo FG
Spiess BD, see Tuman KJ
Springman SR, see Hogan KJ
Spydell J, see Long GW
Stanley TH
  Hague B, Mock DL, Streisand JB, Bubbers S, Dzelzkalns RR, Bailey PL, Pace NL, East KA, Ashburn MA. Oral transmucosal fentanyl citrate (lollipop) premedication in human volunteers, 21
  Leiman BC, Rawal N, Marcus MA, van den Nieuwenhuyzen M, Walford A, Cronau LH, Pace NL. The effects of oral transmucosal fentanyl citrate premedication on preoperative behavioral responses and gastric volume and acidity in children, 328
  see Streisand JB
Steinbach JH, see Stern RC
Steinberg ES, see Pedersen H
Stenqvist O, see Bengston JP
Stern RC, Weiss CI, Steinbach JH, Evers AS. Isoflurane uptake and elimination are delayed by absorption of anesthetic by the Scimed membrane oxygenator, 657
Stevenson GW, see Birmingham PK
Stienstra R, Gielen M, van Poorten F, Kroon JW. Spinal anesthesia with plain bupivacaine 0.5: regression of sensory and motor blockade with different temperatures of the anesthetic solution, 593
Stohler CS, see Van Der Spek AFL
Stojanov L, see Radošević-Stašić B
Stokke T, see Reiestad F
Stone DJ, DiFazio CA. Alfentanil partition coefficient (letter), 850
Stone T, see Harioka T
Streisand JB
  Stanley TH, Hague B, van Vreeswijk H, Ho GH, Pace NL. Oral transmucosal fentanyl citrate premedication in children, 28
  see Stanley TH
Stromskag KE, Steen PA. Interpleural anesthesia for extracorporeal shock wave lithotripsy (letter, reply), 552
Sugiyama D, Nobuhara K, Maekawa N, Obara H. Severe lightning pain after spinal anesthesia in a patient with tabes dorsalis (letter), 268
Sum-Ping ST, Mehta MP, Anderton JM. A comparative study of methods of detection of esophageal intubation, 627
Sundaram P, see Ho LC
Swanson GA, see Hoffmann CO
Swen J, Rashkovsky OM, Ket JM, Koot HWJ, Hermans J, Agoston S. Interaction between nondepolarizing neuromuscular blocking agents and inhalation anesthetics, 752
Sword BC. The closed circle method of administration of gas anesthesia. Anesthesia and Analgesia: 1930;9:198-202 (historical note), 322
Szabo MD
  Crosby G. (book review), 426
  Crosby G. Central nervous system effects of magnesium (letter), 691
Szyfelbein SK, see Carr DB

Tadjziechy M, see Pollan S
Taglientie TM, Jayagopal S. Transient left bundle branch block following lidocaine, 545
Takaoka F, see Ramsay MAE
Takaori M, see Fujita Y
Takeshima R, Dohi S. Comparison of arterial baroflex function in humans anesthetized with enflurane or isoflurane, 284
Tanguy A, see Dalens B
Targ AG
  Yasuda N, Eger EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in plastics and rubber composing a conventional anesthetic circuit, 218
  see Yasuda N
Tatemichi TK, see Young WL
Teller LE, see Alexander CM
Theissen JL, see Brussel T
Thoms H. Walter Channing and the introduction of anesthesia in childbirth. Anesthesia and Analgesia: 1932;11:1-4 (historical note), 244
Till W, see Kennedy RW
Tinker JH, see Pearson KS
Tirer S. (book review), 694
Toda H, see Harioka T
Todd DP. Poststernotomy neuralgia: a new pain syndrome (letter), 692
Todd G, see Coventry DM
Tomlinson DL, Goto H, Graf JC, Arakawa K. Incidental discovery of persistent left superior vena cava during cardiac surgery, 393
Topsis J, Kinas HY, Kandall SR. Esophageal perforation-a complication of neonatal resuscitation, 532
Traber DL. (book review), 693
Trépanier CA, see Lessard MR
Truog RD, Rice SA. Inorganic fluoride and prolonged isoflurane anesthesia in the intensive care unit, 843
Tucker GT, see Lee A
Tullock WC, see Wilks DH
Tuman KJ, Spiess BD, McCarthy RJ, Ivankovich AD. Comparison of viscoelastic measures of coagulation after cardiopulmonary bypass, 69
Turk P, see De Soto H

Turnbull AD, see Acampora GA

Udovic-Širola M, see Radošević-Stašić B
Uebel R, see Coetzee A
Ueda I, see Nosaka S
Uejima T, see Birmingham PK
Ullman DA, see Schmitt LG
Upton RN, see Rutten AJ
Uy NTL, see Melnick B

Van Aken H, see Brussel T
van den Nieuwenhuyzen M, see Stanley TH
Van Der Spek AFL, Reynolds PI, Ashton-Miller JA, Stohler CS, Schork MA. Differing effect of agonist and antagonist muscle relaxants on cat jaw muscles, 76
van Poorten F, see Stienstra R
van Vreeswijk H, see Streisand JB
Vandam LD. Sciatica and the cerebral spinal fluid (letter), 261
Vanneuville G, see Dalens B
Vedrinne C, Vedrinne JM, Guiraud M, Patricot MC, Bouletreau P. Nitrogen-sparing effect of epidural administration of local anesthetics in colon surgery, 354
Vedrinne JM, see Vedrinne C
Venneuville G, see Dalens B
Viars P, see Mouren S
Vidal F, see Canet J
Vigfusson G, see Brussel T
Vincent J-L, see Armistead CW Jr
Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanyl synergism for anesthetic induction in patients, 213
Vukelich GR, see Bragg CL

Wakefield ML, see Dubin SA
Walford A, see Stanley TH
Walker S, see Fink BR
Wall RT. (book review), 427
Wallenfang T, see Jantzen JP
Wallin G, see Lundin S
Ward DS, see Abdul-Rasool IH
Ward PA, see Kennedy TP
Warltier DC, see Schmeling WT
Warner LO, Bremer DL, Davidson PJ, Robers GL, Beach TP. Effects of lidocaine, succinylcholine, and tracheal intubation on intraocular pressure in children anesthetized with halothane-nitrous oxide, 687
Warner MA, see Warner ME
Warner ME, Warner MA, Narr BJ. Difficult laryngoscopy and diabetes mellitus (letter), 550
Waskell L, see Gauntlett IS
Waymack JP, Miskell P, Gonce S. Alterations in host defense associated with inhalation anesthesia and blood transfusion, 163
Weakly JN, see Goldberg ME
Wedel DJ, see Atchison SR
Weiss CI, see Stern RC
Weissman C, see Pantuck EJ
Whelan E, Wood AJJ, Shay S, Wood M. Lack of effect of spinal anesthesia on drug metabolism, 307
Wilcosky B Jr, see Burgess FW
Wilks DH, Tullock WC, Klain M. Airway obstruction caused by a kinked Hi-Lo Jet^R endotracheal tube durin high frequency jet ventilation, 116
Willock MM, see Bourke DL
Wilson PR, see Atchison SR
Wilton NC, see Reynolds PI
Wium C, see Coetzee A
Wolpert L, see Landers DF
Wong KC
  see Landers DF
  see Nosaka S
Wood AJJ, see Whelan E
Wood DA. Survey of anesthesia given in 550 brain operations in the years 1921 to 1930 inclusive. Anesthesia and Analgesia: 1932;11:201-5 (historical note), 14
Wood M, see Whelan E
Wooten DJ, see King H-K
Wright AJ
  Theodore Dreiser's "Laughing Gas," 39
  see Lell WA
Wynn RL, see Rudo FG

Xavier AV, see Kissin I

Yaksh TL, see Sosnowski M
Yasuda N
  Targ AG, Eger EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissue, 370
  see Targ AG
Yee LL, see Heerdt PM
Yoshitake J, see Hoka S
Young WL, Gitelman DR, Tatemichi TK, Prohovnik I. Acute left bundle branch block precipitated by trimethaphan (letter), 413
Youngstrom PC. (book review), 426

Zimpfer M, see Mayer N

Subject Index

- **Activated coagulation time**, see Blood, coagulation
- **Air**, see Embolism
- **Alfentanil**
  - see Analgesics
  - see Anesthetics, intravenous
- **Allergy**
  - anaphylaxis
    - cimetidine treatment (letter), 264
  - fibrin glue, 684
- **Ambulatory anesthesia**, see Anesthesia, outpatient
- **Amino acids**
  - see Metabolism
  - see Protein
- **Aminophylline**, see Pharmacology
- **Ammonia**, see Metabolism
- **Analgesics**
  - alfentanil
    - hemodynamic changes, atropine and glycopyrrolate effects on, 386
    - midazolam, synergism with, 213
    - partition coefficients (letter), 850
  - buprenorphine
    - urodynamic effects, 348
  - fentanyl
    - autotransfusor, removal from blood, 239
    - carotid body reflex, 756
    - intrathecal, for labor, 122
    - oral transmucosal, premedication, 21
    - oral transmucosal, premedication, in children, 28
    - urodynamic effects, 348
  - morphine
    - intrathecal, for labor, 122
    - intrathecal administration, spinal cord distribution, 323
    - postoperative pain management, epidural compared to patient-controlled intravenous, 826
  - pentamorphone
    - antinociceptive activity of, compared to fentanyl and morphine, 450
  - sufentanil
    - negative chronotropic actions, 4
    - ventilatory and cardiovascular responses to, isoflurane and, 300
- **Anaphylaxis**, see Allergy
- **Anatomy**
  - dura mater, 768
- **Anesthesia**
  - cardiovascular
    - costs, 336
    - membrane oxygenators, isoflurane uptake and elimination, 657
  - electroconvulsive therapy
    - T-wave changes associated with, 677
  - intravenous
    - droperidol, delayed side effects in ambulatory anesthesia, 748
  - local
    - bupivacaine, induced cardiac arrest, resuscitation from, 403
  - neonatal
    - resuscitation, esophageal perforation, 532
  - neurosurgery
    - monitoring of cranial nerves, 242
  - obstetric
    - cesarean section, air embolism during, 620
    - cesarean section, visceral pain, 46
    - hypotension, following epidural anesthesia, 604
    - labor, intrathecal fentanyl, morphine, 122
    - laryngeal atresia in newborn, 535
    - neonatal resuscitation, esophageal perforation, 532
    - postoperative breast-feeding and neonatal drug levels, 400
  - orthopedic
    - air embolism, during Harrington instrumentation, 132
    - isoflurane, enflurane, hypotensive, catecholamine and renin angiotensin responses to, 467
  - outpatient
    - droperidol, delayed, 748
    - pediatric, malignant hyperthermia, 846
  - pediatric
    - benzyl alcohol toxicity (letter), 855
    - esophageal temperature, inspired gas warming, 192
    - intraoperative temperature monitoring sites, 192
    - malignant hyperthermia, myoglobinuria, 846
    - penile block, via subpubic space, 41
    - premedication, fentanyl citrate, oral transmucosal, 28
    - regional (editorial), 697
    - spontaneous ventilation, assessment, 484
    - temperatures, inspired gas humidification, effects, 783
  - urologic
    - lithotripsy, hemoptysis in child during, 526
- **Anesthetic techniques**
  - circle and semiopen circuits
    - spontaneous ventilation with, 484
  - closed circuit systems
    - humidity of, 83
  - endobronchial
    - biphasic carbon dioxide elimination waveform with, 829
    - cuff pressures, of double-lumen tubes, bronchial rupture and, 608
    - endotracheal tube extension for (letter), 548
  - epidural
    - back pain, Nesacaine-MPF, 113
    - blood patch, postdural puncture headache prevention, 522
    - bupivacaine, motor and sensory block, 739
    - cardiovascular effects, 174
    - catheters, securing of (letter), 856
    - catheters, stylet disposal (letter), 411
    - etidocaine, motor and sensory block, 739
    - lidocaine, tachyphylaxis, 180
    - mepivacaine, motor and sensory blockade, 739
    - morphine, postoperative pain relief, compared with patient-controlled intravenous, 826
    - narcotics, outpatient pain treatment (letter), 408
    - needle, advancement (letter), 691
    - needle, inability to thread catheter (letter), 267
    - nitrogen-sparing effects, 354
    - obstetric, hypotension following, 604
    - sympathetic block, intraneural recordings in, 788
    - thoracic, central hemodynamic effects, unstable angina, 558
    - thoracic, hemodynamic function and oxygen supply-demand relationship, 360
    - thymectomy, in myasthenia gravis, 529
    - treatment of angina (editorial), 555
  - hypotensive
    - enflurane, isoflurane, catecholamine and renin-angiotensin responses, 467
    - isoflurane, blood loss and number of transfusion effects, in orthognathic surgery, 379
    - nitroprusside, esmolol potentiation of, 202
    - trimethaphan, left bundle branch block (letter), 413
  - regional
    - celiac plexus block, for hepatic arterial embolization, intravenous morphine comparison with, 398
    - femoral nerve block, 705
    - interpleural, bupivacaine, for postoperative pain during lactation, 400
    - interpleural, for extracorporeal shock wave lithotripsy (letter), 551
    - interpleural, upper extremity reflex sympathetic dystrophy treatment with, 671

    - intravenous, Bier block, interaction of lidocaine and hypothermia, 53
    - lumbar plexus block (letter), 852
    - lumbar plexus block, fascia iliaca block, 705
    - penile block, via subpubic space, in children, 41
    - sciatic nerve block (letter), 260, 262
  - spinal
    - bupivacaine, temperature, sensory and motor blockade and, 593
    - bupivacaine, time-courses of zones of differential sensory blockade during, 342
    - bupivacaine, visceral pain during cesarean section effects, 46
    - buprenorphine, urodynamic effects, 348
    - dibucaine, duration, epinephrine effects on, 819
    - drug metabolism effects, 307
    - dura mater fibers orientation in, 768
    - fentanyl, for labor, 122
    - fentanyl, urodynamic effects, 348
    - hypobaric, level and duration of, injection rate effect on, 496
    - impulse transmission during, 15
    - lightning pain, in tabes dorsalis (letter), 268
    - morphine, for labor, 122
    - morphine, spinal cord distribution, 323
    - needles, transdural fluid leak rate determination by, 457
    - neuropeptides, clinical uses (letter), 416
    - pain, tourniquet (letter), 410
    - pancuronium, subarachnoid injection, 516
    - tetracaine, time-courses of zones of differential sensory blockade, 342

- **Anesthetics, gases**
  - nitrous oxide
    - intravenous, thiopental prolongation of survival in hypoxia and (letter), 408
    - left ventricular function and atrial elastance effects, halothane-fentanyl-pancuronium and, 313
    - nerve palsies after (letter), 136
    - sympathetic outflow augmentation by, 444
    - Theodore Dreiser's "Laughing Gas," 391
- **Anesthetics, intravenous**
  - alfentanil
    - midazolam synergism with, 213
  - diazepam
    - first-pass uptake, in lung, 461
  - etomidate
    - hemodynamic and cardiodynamic effects, 35
    - myoclonus associated with, 256
  - fentanyl
    - atrial natriuretic factor plasma level effects (letter), 549
    - near-awakening from, 169
  - ketamine
    - malignant hyperthermia and, 501
  - midazolam
    - synergism with alfentanil, 213
  - propofol
    - atrioventricular Mobitz I block during, 524
    - hemodynamic and cardiodynamic effects, 35
    - hemodynamic changes associated with, atropine and glycopyrrolate effects on, 386
    - plasma concentrations, myocardial contractility and left ventricular afterload effects, 473
  - sufentanil
    - negative chronotropic actions, 4
  - thiopental
    - first-pass uptake, in lung, 461
    - halothane, isoflurane hepatotoxicity and, 491
- **Anesthetics, local**
  - 2-chloroprocaine
    - intrathecal, neurologic deficit following, 113
  - bupivacaine
    - celiac plexus block, for hepatic arterial embolization, 398
    - epidural, motor and sensory blocks after, 739
    - intravenous, hemodynamic and central nervous system effects, 291
    - intravenous, toxic doses, cardiovascular effects and mechanisms of death, 276
    - myocardial contractility, depression mechanisms, 732
    - pharmacokinetics, time-dependent changes in (letter), 423
    - smooth muscle contraction, 504
    - spinal, temperature, sensory and motor blockade and, 593
    - spinal, time-courses of zones of differential sensory blockade, 342
    - toxicity, compared with ropivacaine, 563
    - visceral pain during cesarean section, 46
  - cocaine
    - toxicity, esmolol management of, 663
  - dibucaine
    - spinal, duration, epinephrine effects on, 819
  - etidocaine
    - epidural, motor and sensory blocks after, 739
  - lidocaine
    - interaction with hypothermia, in Bier blocks, 53
    - intraocular pressure effects, in children, 687
    - intravenous, hemodynamic and central nervous system effects, 291
    - intravenous, toxic doses, cardiovascular effects and mechanisms of death, 276
    - left bundle branch block following, 545
    - smooth muscle contraction effects, 5
  - mepivacaine
    - epidural, motor and sensory blocks, 739
  - ropivacaine
    - disposition kinetics, 736
    - intravenous, hemodynamic and central nervous system effects, 291
    - intravenous, toxic doses, cardiovascular effects and mechanisms of death, 276
    - toxicity, compared with bupivacaine, 563
  - tetracaine
    - hypobaric, level and duration of, injection rate effects on, 496
    - smooth muscle contraction effects, 5
    - spinal, time-courses of zones of differential sensory blockade during, 342
  - toxicity
    - bupivacaine, convulsant and supraconvulsant doses, 794
    - ropivacaine, convulsant and supraconvulsant doses, 794
- **Anesthetics, volatile**
  - desflurane
    - solubility, in human tissue, 370
    - solubility, in plastics and rubber composing anesthetic circuit, 218
  - diethyl ether
    - acetylcholine, histamine, phenylephrine bronchoconstriction and, 226
  - enflurane
    - atrial baroflex function effects, 284
    - contractile response of trachealis muscle, 60
    - hemodynamic changes and oxygen consumption in burned patient, 43
    - hypotensive, catecholamine and renin-angiotensin responses, 467
  - halothane
    - allogeneic sarcoma growth, 570
    - heart conduction system effects, 721
    - hepatic cell ultrastructure effects, compared with isoflurane, 491
    - intravenous injection, toxicity, 250
    - solubility, in human tissue, 370
    - solubility, in plastics and rubber composing anesthetic circuit, 218
    - succinylcholine administration during jaw muscle effects, 76
  - I-653
    - solubility, in human tissue, 370
    - solubility, in plastics and rubber composing anesthetic circuit, 218

- isoflurane
  - atrial baroflex function effects, compared with enflurane, 284
  - hemodynamic changes and oxygen consumption in burned patient, 431
  - hepatic cell ultrastructure effects, compared with halothane, 491
  - hypotensive, blood loss in orthognathic surgery, 379
  - hypotensive, catecholamine and renin-angiotensin responses, 467
  - inorganic fluoride concentrations, 843
  - metabolism, isoniazid, effects, 245
  - myocardial necrosis, 575
  - near-awakening from, 169
  - solubility, in human tissue, 370
  - solubility, in plastics and rubber, 218
  - uptake and elimination, membrane oxygenators, 657
  - ventilatory and cardiovascular responses to sufentanil, 300
- methoxyflurane
  - host defense alterations, 163
- sevoflurane
  - solubility, in human tissue, 370
  - solubility, in plastics and rubber composing anesthetic circuit, 218

Angina
- see Heart
- see Pain

Angiotensin
- see Enzymes
- see Polypeptides

Antagonists
- narcotic
  - naloxone, CO_2 levels and (letter), 421

Anxiety, see Psychological responses

Aspiration
- see Complications
- see Gastrointestinal tract, stomach
- see Lung

Atracurium, see Neuromuscular relaxants

Atrial natriuretic factor, see Polypeptides

Atropine, see Parasympathetic nervous system

Autotransfusion, see Transfusion

Baroreceptors
- see Receptors
- see Reflexes

Benzodiazepines, see Hypnotics

Benzyl alcohol, see Toxicity

Bier block, see Anesthetic techniques, regional intravenous

Biotransformation, drug
- amino acid parenteral nutrition effects on, 727
- propranolol
  - spinal anesthesia, 307

Block
- see Anesthetic techniques, regional, spinal, epidural
- see Heart

Blood
- coagulation
  - ACT (letter), 142
  - fibrin glue, anaphylactic reaction to, 684
  - viscoelastic measures of, after cardiopulmonary bypass, 69
- hemodilution
  - cardiovascular effects, 174
- platelets
  - thrombocytopenia, pseudothrombocytopenia, in elderly patient, 396

Blood pressure
- hypertension
  - cardiogenic, chemoreflex, 633
- hypotension
  - isoflurane-induced, blood loss and number of transfusions effects, in orthognathic surgery, 379
- measurement
  - oscillometric, from adult thumb, 668
- monitoring
  - during CPR, disposable device for (letter), 418
- reflex control
  - (editorial), 273
  - enflurane, isoflurane effects, 284

Book reviews
- Anesthesia and the Heart Patient (Estafanous FG) [Bashein C], 270
- Anesthesia and the Lung (Stanley T, Sperry R) [Goldman JM, Brown P], 695
- Anesthesia in Obstetrics and Gynecology, Vol 3, No 1 of Problems in Anesthesia Series (Hood DD) [Youngstrem PC], 427
- Anesthesiology Clinics of North America Management of Postoperative Pain (Oden RV) [Wall RT], 427
- Cancer Pain (Abram SE) [de Jong RH], 270
- Cardiac Monitoring, Anesthesiology Clinics of North America, December 1988 (Barash PG) [Diaz JH], 695
- Cardiopulmonary Bypass: Current Concepts and Controversies (Tinker JN) [Lell WA, Wright AJ], 859
- Cardiovascular Anesthesia and Postoperative Care, 2nd Edition (Tarhan S) [Quinlan JJ], 696
- Clinical Anatomy for Anesthesiologists (Snell RS, Katz J) [Rorie DK], 271
- Clinical Anesthesia (Barash PG, Cullen BF, Stoelting RK) [Azar I], 145
- Effective Hemostasis in Cardiac Surgery (Ellison N, Jobes DR) [Davis RF], 146
- General Anaesthesia, 5th Edition (Nunn JF, Utting JE, Brown BR Jr) [Ellison N], 145
- Illustrated Manual of Regional Anesthesia (Raj P, Nolte H, Stanton-Hicks M) [Gissen AJ], 147
- Molecular Biology and Cellular Mechanisms of Septic Shock, Progress in Clinical and Biological Research, Volume 286 (Roth BL, Nielsen TB, McKee AE) [Traber DL], 693
- On Chloroform and Other Anaesthetics: Their Action and Administration (Snow J) [Gild W], 694
- Risk and Outcome in Anesthesia (Brown DL) [Gild W], 694
- Surgery for Anaesthetists (Zorab JSM) [Ballinger CM], 693
- Textbook of Pediatric Anesthetic Practice (Tindall B) [Pascucci RC], 859
- Transplant Surgery Anaesthesia and Perioperative Care (Volume 16, Monographs in Anaesthesiology) (Farman JV) [Kang Y], 860
- Yearbook of Anesthesia (Miller RD, Kirby RR) [Szabo MD, Crosby G], 426

Books received, 696

Brain
- electroencephalography
  - near-awakening from isoflurane and fentanyl determination by, 169
- endorphins
  - pituitary-adrenal stress response and, 197
- evoked potentials
  - impulse transmission during spinal anesthesia measurement by, 15
- pituitary-adrenal and hypothalamic pituitary connections, absence of, stress response in, 197

Breathing, see Ventilation

Bronchi, see Lung

Bullous pemphigoid, see Complications

Bupivacaine, see Anesthetics, local

Bupremorphine, see Analgesics

Burns, see Complications

Calcium, see Ions

Cancer
- chemotherapy
  - doxorubicin, cardiovascular collapse and (letter), 138
- halothane and, 570

Carbon dioxide
- capnography
  - biphasic waveform, 829
- hepatic circulation and (editorial), 149
- hypercarbia
  - splanchnic circulation and hepatic function effects, 152
- hypocarbia
  - splanchnic circulation and hepatic function effects, 152

Cardiovascular system
- see Anesthesia, cardiovascular
- see Heart
- see Reflexes

  see Surgery
  see Veins
Carotid bodies, see Receptors, chemo
Catheters, see Equipment
Celiac plexus, see Anesthetic techniques, regional
Cerebrospinal fluid
  sciatica and (letter), 261
Cesarean section, see Anesthesia, obstetric
Chemoreceptors, see Receptors
Children, see Anesthesia, pediatric
2-Chloroprocaine, see Anesthetics, local
Cimetidine
  see Gastrointestinal tract, stomach
  see Pharmacology
Circuits, see Equipment, anesthesia circuits
Clonidine, see Sympathetic nervous system, pharmacology
Coagulation, see Blood
Cocaine, see Anesthetics, local
Colloid, see Fluid balance
Complications
  aspiration
    acid, 87
    gastric pH and volume and (letter), 417
  bullous pemphigoid
    anesthetic management of, 537
  burns
    hemodynamic changes and oxygen consumption during enflurane or isoflurane anesthesia, 431
  diabetes
    difficult laryngoscopy (letter), 550
    tracheal intubation, difficult (letter), 419
  disconnections
    prevention (letter), 414
  headache
    after dural puncture, prevention, epidural blood patch for, 522
  laryngeal atresia
    in newborn, management, 535
  long thoracic nerve palsy, 614
  myasthenia gravis
    sensitivity to pancuronium in, 840
    transsternal thymectomy in, thoracic epidural anesthesia for, 529
  obesity
    preoxygenation, Beelzebub nitrogen and (letter), 850
  sinusitis
    prolonged nasotracheal intubation and, 50
  tracheal tube obstruction, 116
Conduction, see Heart
Conduction anesthesia, see Anesthetic techniques, regional
Cornea, see Eye
Corticosterone, see Hormones
Costs, see Economics
Crystalloids, see Fluid balance
Cyclosporin, see Immune responses, suppression
Cylinders, see Equipment

Dental, see Surgery
Diabetes
  see Complications
  see Metabolism
Dibucaine, see Anesthetics, local
Diethyl ether, see Anesthetics, volatile
Diltiazem
  see Heart
  see Pharmacology
Disconnections, see Complications
Dorsal horn, see Spinal cord
Doxorubicin, see Cancer, chemotherapy
Dreiser, Theodore, see History
Dura mater
  see Anatomy
  see Anesthetic techniques, spinal

Economics
  costs of monitoring
    cardiac surgery, 336
Education
  aphorisms (letter), 141
  specialty training (editorial), 1
  writing
    clarity (letter), 413
Electrocardiography
  see Heart
  see Monitoring
Electroconvulsive therapy, see Anesthesia
Embolism
  air
    cesarean section, head-up tilt and, 620
    during Harrington instrumentation, 132
    during hip arthrography (letter), 264
Endobronchial
  see Anesthetic techniques
  see Equipment, tubes
Endotracheal
  see Anesthetic techniques
  see Equipment, tubes
  see Intubation, tracheal
Enflurane, see Anesthetics, volatile
Enzymes
  angiotensin converting
    enalaprilat, in congestive heart failure, 833
Epidural
  see Anatomy
  see Anesthetic techniques
Equipment
  ampules
    labeling, imprecise (letter), 137
  anesthesia circuits
    Bain, humidity of, 83
    circle, humidity of, 83
    circle, spontaneous ventilation with, 484
    closed, low flow, I-653, sevoflurane, isoflurane and halothane induction and recovery and, 218
    Jackson-Rees, spontaneous ventilation with, 484
  blood pressure monitor
    disposable device (letter), 418
  catheters
    epidural, inability to thread through needle (letter), 267
  cylinders, oxygen
    contaminated, 674
  Eschmann Introducer
    modification, for end-tidal carbon dioxide measurement, 129
  gloves
    reinforced, AIDS infection protection by (letter), 407
  humidifiers
    impedance to breathing effects, 374
  inhalers
    anesthetic adapter for (letter), 266
  IV infusion bag
    diffusion of felt-tip marker pen ink into (letter), 412
  laser surgery, 802
  marker ink
    diffusion into intravenous bag (letter), 412
  tourniquets
    hypothermia and (letter), 549
    response to deflation, 541
  tubes, endobronchial
    double-lumen, cuff pressures, bronchial rupture and, 608
  tubes, endotracheal
    kinked, airway obstruction from, 116
    laser surgery, 802
    oral, damage to (letter), 552
Errata, 147
Esmolol
  see Heart
  see Sympathetic nervous system, pharmacology
Esophagus, see Gastrointestinal tract
Ether, see Anesthetics, volatile, diethyl ether
Etidocaine, see Anesthetics, local
Etomidate, see Anesthetics, intravenous
Evoked potentials, see Brain
Extradural, see Anesthetic techniques, epidural
Eye
  cornea
    abrasion, during anesthesia, 384
  intraocular pressure
    lidocaine, succinylcholine and tracheal intubation effects, in children, 687
    nitroglycerine, succinylcholine and (letter), 139

Famotidine
  see Gastrointestinal tract, stomach
  see Histamine

- **Femoral nerve**
  - see Anatomy
  - see Anesthetic techniques, regional
  - see Nerves
- **Fentanyl**
  - see Analgesics
  - see Anesthetics, intravenous
- **Fibrin**, see Blood, coagulation
- **Fluid balance**
  - colloid
    - hydroxyethyl starch (editorial), 699
  - crystalloid
    - hypertonic saline (editorial), 699
  - in septic shock, 714
- **Fluoride**, see Ions

- **Gastrointestinal tract**
  - esophagus
    - perforation, neonatal, during resuscitation, 532
  - stomach
    - famotidine effects on, 680
    - pH and volume, cut-off values (letter), 417
    - ranitidine effects on, 680
- **Gloves**, see Equipment
- **Glycine**, see Metabolism
- **Glycopyrolate**, see Parasympathetic nervous system

- **Halothane**, see Anesthetics, volatile
- **Headache**, see Complications
- **Heart**
  - angina
    - treatment with epidural block (editorial), 555
  - asystole
    - mitral valve prolapse, after needle puncture, 126
  - block
    - left bundle branch, following lidocaine, 545
    - right bundle branch, trimethaphan precipitated (letter), 413
  - chemoreflexes
    - hypertensive, 633
  - conduction
    - atrioventricular, halothane effects, 721
  - diltiazem
    - sufentanil, vecuronium effects, 4
  - end-systolic pressure-length relationships
    - nitrous oxide, halothane-fentanyl, pancuronium and, 313
  - ischemia
    - isoflurane effects, 575
    - thoracic epidural, central hemodynamic effects, 558
  - myocardial function
    - esmolol potentiation of nitroprusside-induced hypotension, 202
    - propofol effects, 473
  - myocardium
    - contractility, bupivacaine-induced depression, 732
  - propranolol
    - sufentanil, vecuronium effects, 4
  - rhythm
    - cardiac pacing, noninvasive transcutaneous, 229
- **Hemodilution**, see Blood
- **Histamine**
  - cimetidine (letter), 264
  - famotidine
    - gastric volume and pH effects, compared to ranitidine, 680
  - H_2 blockers
    - ranitidine, atracurium-induced neuromuscular blockade and, 611
    - ranitidine, gastric volume and pH effects, compared to famotidine, 680
- **Historical Notes**
  - McMechan FH, McMechan L: Elmer Isaac McKesson, MD, Anesthetist: His life and work. Anesthesia and Analgesia: 1937;16:1–6 [259]
  - Rovenstine EA: Anesthesia: Organization for teaching. Anesthesia and Analgesia: 1937;16:318–22 [118]
  - Sword BC: The closed circuit method of administration of gas anesthesia. Anesthesia and Analgesia: 1930;9:198–202 [322]
  - Thoms H: Walter Channing and the introduction of anesthesia in childbirth. Anesthesia and Analgesia: 1936;11:1–4 [244]
- **History**
  - Theodore Dreiser
    - "Laughing Gas," 391
- **Hormones**
  - corticosterone
    - pituitary-adrenal stress response and, 197
  - prostaglandin E_1
    - intrapulmonary shunt fraction effects, 665
- **Humidification**
  - intraoperative
    - pediatric, temperature, 783
- **Humidifiers**, see Equipment
- **Hydroxyethyl starch**, see Fluid balance, colloid
- **Hypercarbia**, see Carbon dioxide
- **Hypertension**, see Blood pressure
- **Hyperthermia**
  - malignant
    - caffeine halothane muscle contracture test, standardization of, 511
    - caffeine halothane muscle contracture test, standardization of (editorial), 429
    - contracture testing protocol, standardization of, 437
    - in hemodialysis patient, 119
    - ketamine and, 501
    - myoglobinuria in pediatric patients, 846
- **Hypnotics**
  - benzodiazepines
    - midazolam, sedation, aminophylline reversal of (letter), 268
    - midazolam, synergism with alfentanil, 213
- **Hypocarbia**, see Carbon dioxide
- **Hypothalamus**, see Brain
- **Hypoxia**
  - postoperative
    - factors influencing, 207

- **Immune response**
  - halothane and, 570
  - inhalation anesthesia effects, 163
  - suppression
    - cyclosporine, in liver transplantation, 773
  - transfusions effect, 163
- **Induction**
  - anesthesia
    - alfentanil, midazolam synergism with, 213
    - midazolam, synergism with alfentanil, 213
- **Infection**
  - avoidance
    - AIDS, reinforced gloves and (letter), 407
  - effects of transfusions and inhalation anesthesia, 163
  - sinusitis
    - prolonged nasotracheal intubation and, 50
  - syphilis (letter), 268
- **Infusion sets**, see Equipment
- **Inhalers**, see Equipment
- **Interactions, drug**
  - benzodiazepines, opioids, 213
- **Interpleural**, see Anesthetic techniques, regional
- **Intraocular pressure**, see Eye
- **Intrapleural**, see Anesthetic techniques, regional, interpleural
- **Intravenous anesthesia**, see Anesthetic techniques, intravenous
- **Introducer, Eschmann**, see Equipment
- **Intubation**
  - endobronchial
    - endotracheal tube extension for (letter), 548
  - tracheal
    - blind, by monitoring end-tidal CO_2 (letter), 412
    - diabetes and (letter), 550
    - in diabetes (letter), 419
    - Eschmann Introducer modification for, 129
    - methods of detection, 627
    - mivacurium, succinylcholine, in outpatient surgery, 93

- nasal, prolonged, paranasal sinus inflammation and, 50
- nasal, safety, adapter for (letter), 135

Ions
- calcium
  - tissue function control, 100
- fluoride
  - concentrations, isoniazid effects on, 245
- magnesium
  - central nervous system effects on (letter), 691
- serum potassium
  - T-wave changes and, electroconvulsive therapy and, 677

Isoflurane, see Anesthetics, volatile

Isoniazid, see Pharmacology

Jehovah's Witnesses
- see Medicolegal
- see Organizations

Kidney
- failure
  - malignant hyperthermia in, 119
- transplantation
  - orthoclone, adverse responses to, 822
- urodynamics
  - spinal opioids effects, fentanyl, buprenorphine, 348

Larynx
- atresia
  - in newborn, management of, 535

Laser, see Surgery

Lidocaine, see Anesthetics, local

Lithotripsy
- see Anesthesia, urologic
- see Surgery, urologic

Liver
- blood flow
  - carbon dioxide and (editorial), 149
  - hypocapnia and hypercapnia, effects on, 152
- cirrhosis
  - glycine and ammonia metabolism in, 776
- function
  - hypocapnia and hypercapnia effects on, 152
- hepatotoxicity
  - halothane, 491
  - isoflurane, 491
- transplantation
  - coronary spasm during (letter), 854
  - cyclosporine efficacy in, 773

Local anesthetics, see Anesthetics, local

Long thoracic nerve, see Nerve

Lumbar plexus, see Anesthetic techniques, regional

Lung
- adult respiratory distress syndrome, pulmonary surfactant and, 805
- aspiration
  - acid, 86
- bronchi
  - bronchoconstriction, ether and, 226
- drug uptake
  - verapamil, diazepam, thiopental, 461
- trachea
  - muscle tone, enflurane effects on, 60

Magnesium, see Ions

Malignant hyperthermia, see Hyperthermia

Measurement techniques
- blood pressure
  - oscillometric, from adult thumb, 668
- electroencephalography
  - near-awakening from isoflurane and fentanyl determination by, 169
- electromyography
  - abdominal muscle activity, intraabdominal pressure effects, 598
- oximetry
  - buccal sensor for (letter), 417
  - comparisons in (letter), 851
- pulse oximetry
  - fingerprinting ink effect on (letter), 265
  - henna effect (letter), 416
  - probe disconnection (letter), 265
- temperature, pediatric, 192
- ulnar train-of-four stimulation, 242

Medicolegal
- Jehovah's Witnesses
  - transfusion, 647

Mepivacaine, see Anesthetics, local

Metabolism
- ammonia
  - cirrhosis and, 776
- enzyme induction
  - metabolites, isoniazid and, 245
- glycine
  - cirrhosis and, 776
- hypoglycemia
  - thiamine prevention of Wernicke's encephalopathy and (letter), 407
- nutrition
  - amino acids, drug metabolism, 727
  - postoperative, nitrogen balance, epidural anesthesia effects, 354

Methoxyflurane, see Anesthetics, volatile

Midazolam, see Hypnotics, benzodiazepines

Mitral valve, see Heart

Mivacurium, see Neuromuscular relaxants

Monitoring
- blood pressure
  - disposable device, during CPR (letter), 418
- costs
  - cardiac surgery, 336
- mandibular nerve stimulation
  - succinylcholine and, 158
- train-of-four
  - during facial nerve stimulation, 242
  - succinylcholine and, 158
- twitch tension
  - succinylcholine and, 158

Morphine, see Analgesics

Muscle, skeletal
- abdominal
  - pattern of activity postoperatively, intraabdominal pressure effects,

Muscle, smooth
- local anesthetic effects, 504

Naloxone, see Antagonists, narcotic

Needles, see Equipment

Neonates
- see Anesthesia, obstetric
- see Anesthesia, pediatric

Nerve
- evoked potentials
  - lidocaine and hypothermia interacti effects, 53
- long thoracic
  - postoperative palsy, 614
- sciatic
  - pain (letter), 260, 261, 262

Neuromuscular relaxants
- atracurium
  - interaction with inhalational anesthetics, 752
  - ranitidine effects, 611
  - ulnar train-of-four stimulation in fa movement prediction and, 242
- mivacurium
  - tracheal intubating conditions and, outpatient surgery, 93
- pancuronium
  - interaction with inhalation anesthetics, 752
  - sensitivity to, in myasthenia gravis, 840
  - subarachnoid injection of, accident 516
- pipecuronium
  - interaction with inhalation anesthetics, 752
- succinylcholine
  - effects on masseter and adductor pollicis muscles, 158
  - intraocular pressure and, in childre 637
  - intraocular pressure and (letter), 13
  - jaw muscles, effects, 76
  - potassium levels, effects, 677
  - tracheal intubating conditions and, outpatient surgery, 93
- vecuronium
  - continuous infusion, increased requirements for, 518
  - injection rate, 624
  - interaction with inhalation anesthetics, 752
  - jaw muscles, effects, 76
  - negative chronotropic actions, 4

Neuromuscular transmission
- differential effects
  - succinylcholine and, 158

- **Neuropeptides**, see Polypeptides
- **Neurosurgery**
  - see Anesthesia
  - see Surgery
- **Nitroglycerin**
  - see Anesthetic techniques, hypotensive
  - see Pharmacology
- **Nitroprusside**
  - see Anesthetic techniques, hypotensive
  - see Pharmacology
- **Nitrous oxide**, see Anesthetics, gases
- **Nutrition**, see Metabolism

- **Obesity**, see Complications
- **Obstetrics**, see Anesthesia, obstetric
- **Ophthalmology**, see Surgery, ophthalmologic
- **Opioids**, see Analgesics
- **Organizations**
  - Jehovah's Witnesses
    - transfusion, 647
- **Orthoclone**, see Kidney, transplantation
- **Orthopedics**, see Surgery, orthopedic
- **Outpatient anesthesia**, see Anesthesia, outpatient
- **Oximetry**
  - see Measurement techniques
  - see Oxygen, measurement
- **Oxygen**
  - cylinders
    - contaminated, 674
  - measurement
    - oximetry, comparisons in (letter), 851
  - supply/demand ratio
    - epidural anesthesia effects, 360
  - therapeutic
    - arterial desaturation effects, 207

- **Pacing**
  - cardiac, see Heart
- **Pain**
  - angina
    - thoracic epidural central hemodynamic effects and, 558
  - cancer, epidural narcotics, outpatient treatment with (letter), 408
  - deafferentation
    - epidural clonidine in (letter), 424
  - postoperative
    - hepatic arterial embolization, celiac plexus block comparison to intravenous morphine for, 398
    - morphine, epidural compared to patient-controlled intravenous, 826
    - poststernotomy, 81, 692 (letter)
  - pseudosciatica (letter), 261
  - sciatic (letter), 260, 261, 262
  - tourniquet
    - bupivacaine, tetracaine spinal anesthesia and (letter), 410
- **Paralysis**
  - see Muscle, skeletal
  - see Nerve
  - see Neuromuscular transmission
- **Parasympathetic nervous system**
  - atropine
    - propofol, alfentanil hemodynamic changes effects, 386
  - glycopyrrolate
    - propofol, alfentanil hemodynamic changes effects, 386
- **Pediatrics**, see Anesthesia, pediatric
- **Penile block**, see Anesthetic techniques, penile block
- **Pentamorphone**, see Analgesics
- **Peridural**, see Anesthetic techniques, epidural
- **Pharmacokinetics**
  - diazepam
    - first-pass uptake, in lung, 461
  - local anesthetics
    - bupivacaine, time-dependent changes in (letter), 423
  - ropivacaine, 736
  - thiopental
    - first-pass uptake, in lung, 461
  - verapamil
    - first-pass uptake, in lung, 461
- **Pharmacology**
  - aminophylline
    - reversal of midazolam sedation (letter), 268
  - diltiazem
    - sufentanil, vecuronium effects on, 4
  - isoniazid
    - enflurane metabolism and fluoride concentrations and, 245
  - lidocaine
    - tachyphylaxis, 180
- **Pipecuronium**, see Neuromuscular relaxants
- **Pituitary**, see Brain
- **Platelets**, see Blood
- **Polypeptides**
  - atrial natriuretic
    - plasma levels, fentanyl effects on (letter), 549
  - neuropeptides
    - subarachnoid, clinical uses (letter), 416
- **Potassium**, see Ions
- **Premedication**
  - oral transmucosal
    - fentanyl citrate, in children, 28
    - fentanyl citrate (lollipop), 21
- **Preoxygenation**
  - see Oxygen
  - see Ventilation
- **Propofol**, see Anesthetics, intravenous
- **Propranolol**, see Sympathetic nervous system, pharmacology
- **Prostaglandins**, see Hormones
- **Protein**
  - amino acid parenteral nutrition
    - drug metabolism effects, 727
- **Psychological responses**
  - anxiety
    - preoperative, 763
- **Ranitidine**
  - see Gastrointestinal tract, stomach
  - see Histamine
- **Receptors**
  - chemo
    - carotid body, fentanyl inhibition of, 756
  - pressoreceptors
    - enflurane, isoflurane effects, 284
  - spinal cord pain receptors
    - adenosine, hyperesthesia modulation effects, 587
- **Reflexes**
  - baroreceptor
    - arterial blood pressure control and (editorial), 273
    - enflurane, isoflurane effects, 284
  - chemoreceptors
    - cardiac, 633
- **Respiration**, see Ventilation
- **Respiratory distress syndrome**, see Lung
- **Ropivacaine**, see Anesthetics, local

- **Saline**, see Fluid balance, crystalloid
- **Sciatic nerve block**, see Anesthetic techniques, regional
- **Sciatica**, see Pain
- **Serotonin**
  - cardiogenic hypertension elicited by, 633
- **Sevoflurane**, see Anesthetics, volatile
- **Shock**
  - septic
    - resuscitation, fluid (editorial), 699
    - resuscitation, hypertonic saline solution-Hetastarch for, 714
- **Sinusitis**, see Complications
- **Skeletal muscle**
  - adductor pollicis
    - succinylcholine effects at, 158
  - masseter
    - succinylcholine effects at, 158
- **Smithisms**, see Education, aphorisms
- **Solubility**
  - partition coefficients
    - for anesthetic circuit components, 218
  - volatile anesthetics, 370
- **Spinal anesthesia**, see Anesthetic techniques, spinal
- **Spinal cord**
  - clonidine effects, 185
  - laminae of dorsal horn
    - morphine effects on, 323
  - pain receptors
    - adenosine, hyperesthesia modulation effects, 587
- **Statistics**
  - power (letter), 263
- **Stomach**, see Gastrointestinal tract
- **Succinylcholine**, see Neuromuscular relaxants
- **Sufentanil**
  - see Analgesics
  - see Anesthetics, intravenous
- **Surfactant**, see Lung

Surgery
- abdominal
  - abdominal muscle activity effects on intraabdominal pressure following, 598
- cardiac
  - noninvasive transcutaneous cardiac pacing, 229
- cardiovascular
  - cardiopulmonary bypass, viscoelastic measurement of coagulation after, 69
  - poststernotomy neuralgia, 81
  - poststernotomy neuralgia (letter), 692
- dental
  - orthognathic, isoflurane-induced hypotension in, 379
- laser
  - endotracheal tube for, 802
- orthopedic
  - air embolism, during hip arthrography (letter), 264
- transplantation
  - kidney, orthoclone, adverse responses to, 922
  - liver, coronary artery vasospasm during (letter), 854
  - liver, cyclosporine efficacy in, 773
- urologic
  - lithotripsy, heart synchronized ventilation during (letter), 139
  - transurethral prostatectomy, serum ammonia levels after, 776

Sympathetic nervous system
- pharmacology
  - clonidine, 185, 424 (letter)
  - esmolol, 202
  - nitrous oxide, 444
  - propranolol, 307
- reflex dystrophy
  - upper extremity, interpleural analgesia in treatment of, 671

Teaching, see Education
Techniques
- transcutaneous cardiac pacing, 229

Temperature
- body
  - measurement sites, pediatric, 192
  - tourniquet hypothermia (letter), 549
- hypothermia
  - lidocaine interaction and, in Bier block, 53
- intraoperative
  - pediatric, humidification effects, 783

Tetracaine, see Anesthetics, local
Thiopental, see Anesthetics, intravenous
Thrombocytopenia, see Blood, platelets
Tourniquet
- see Equipment
- see Pain

Toxicity
- benzyl alcohol
  - in neonates (letter), 855
- bupivacaine, 276
  - cardiac, 732
- halothane
  - pulmonary, 250
- local anesthetics
  - bupivacaine, 291, 563, 794
  - lidocaine, 276, 291
  - ropivacaine, 276, 291, 563, 794

Trachea, see Lung
Train of four
- see Measurement techniques
- see Neuromuscular relaxants

Transfusion
- autotransfusor
  - fentanyl removal from blood, 239
- immunologic effects, 163

Transplantation, see Individual organ
Trimethaphan, see Anesthetic techniques hypotensive
Tubes, see Equipment, endotracheal tube

Urology
- see Anesthesia, urologic
- see Surgery

Vecuronium, see Neuromuscular relaxant
Veins
- left superior vena cava, persistent, 393

Vena cava, see Veins
Ventilation
- isoflurane plus sufentanil effects, 300
- responses to tourniquet deflation, 541
- work of breathing
  - impedance, halothane and, 374

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
64th CONGRESS — March 9–13, 1990
Sheraton-Waikiki Hotel • Honolulu, Hawaii

MEETING REGISTRATION, HOTEL RESERVATION, SCIENTIFIC MEETING INFORMATION: Will be mailed in late November to all IARS members. (IARS members outside of North America who plan to attend the meeting will receive this material by airmail upon request.) Non-IARS members should request information from the Cleveland IARS office: 3645 Warrensville Center Road, Cleveland, OH 44122. Tel: (216) 295-1124.

MEETING SCHEDULE: **Registration:** Friday, March 9, 1–6 p.m.
Scientific Program: Saturday–Tuesday, March 13
Exhibits: Saturday–Monday, March 12

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture
Anesthesia Mortality in Perspective
to be given by
Arthur S. Keats, M.D.
Chief, Division of Cardiovascular Anesthesia
Texas Heart Institute
Clinical Professor of Anesthesiology
University of Texas Health Science Center
Houston, Texas

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Jeffrey L. Apfelbaum, MD, Moderator; Raafat S. Hannalah, MD, Harry Wong, MD, Paul F. White, PhD, MD, Kenneth Zahl, MD

QUALITY ASSURANCE:
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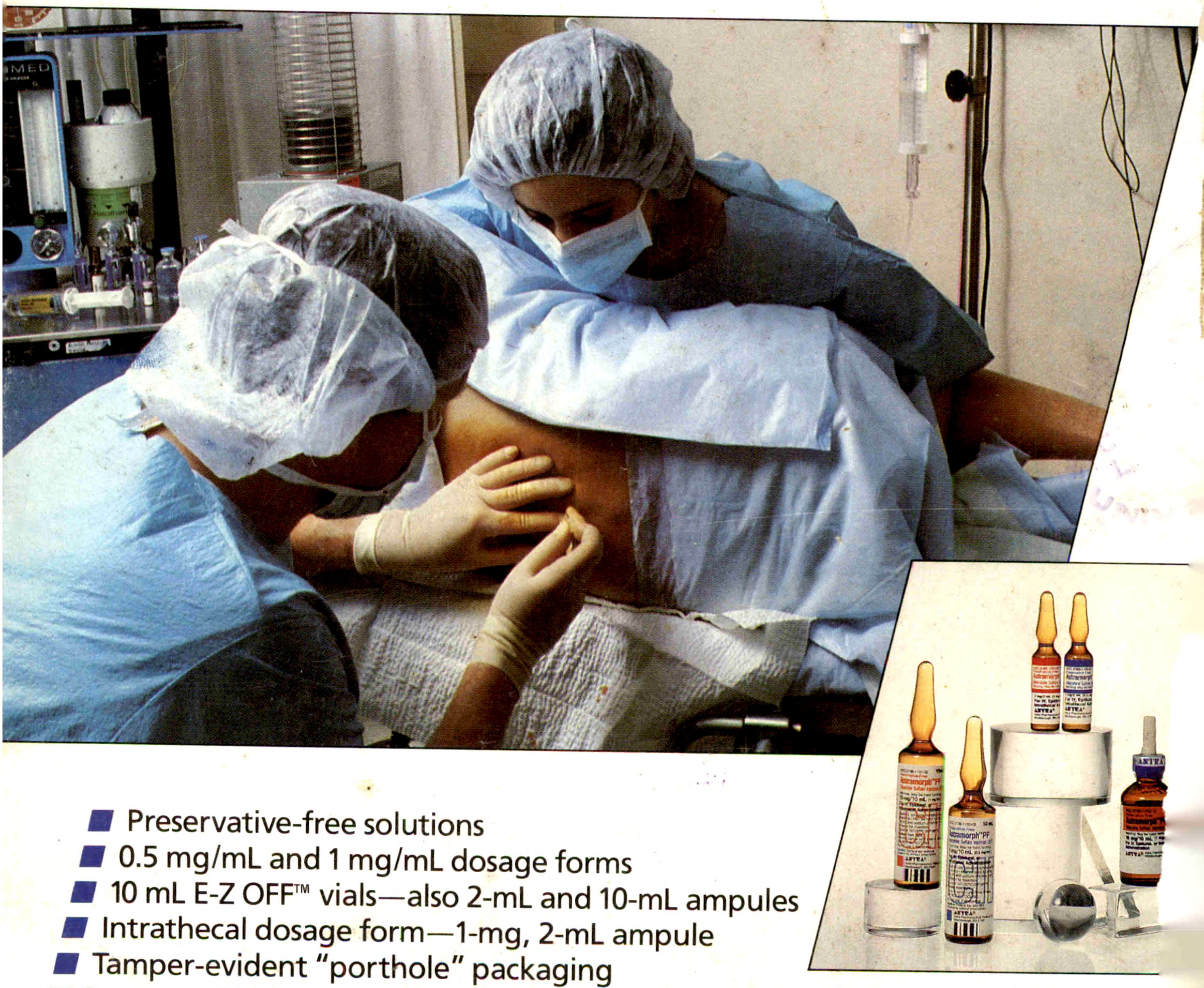

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